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ACCURACY IN PERCENTAGE REPRESENTATION OF HEAVY MINERAL FREQUENCIES

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For years geologists have been aware of the presence, in sediments and sedimentary formations, of a small proportion of minerals common in igneous or metamorphic rocks. An investigation of the occurrence, varieties, etc., of these minerals has led to the conclusion that certain type species may be characteristic of a certain sediment or formation and may be of use both in determining the source of the detrital material making up the formation and in correlating beds containing similar mineral suites. For such purposes, the "heavy minerals"—those resistant species which have a specific gravity greater than about 2.9—have proved to be of greatest value. The methods of indicating the proportions and frequencies of such minerals will be the immediate concern of this paper.

Until almost the present day, workers in heavy minerals have contented themselves to estimate frequencies of the different species present, and to indicate the abundance or scarcity of these species by several well-known devices. Thus, in one "standard" scheme, the numbers one to five are used as indices of frequency—1 indicating a rarity or scarcity, and 5 an abundance or "flood." Those who trust their abilities more use a scale from 1 to 10 with a similar import.

The meaning of the numbers so used is not immediately apparent. Some workers conceive of the numbers 1 to 5, for example, as representing roughly percentages, but surely it seems unlikely that "one" should ever stand for 20% or "five" for 100%. For certain workers, "one" usually denotes rarity, that is, one or, at most, a few grains of that species present. Two denotes 5–10 grains, 3 about 10% of the slide, 4 about 30–50% and 5 above 50% or "flood." Other workers attach different meanings to the same numbers. Using this "1–5" representation, there is no doubt that an experienced worker can assign frequencies to the different species more or less correctly by estimation. When the numbers 1–10 are used there may be raised a question as to the reliability of the apparent increase

in accuracy. However, apart from criticisms concerning largely the personal ability of the worker, the general method above described is open to at least two objections:

(*a*) The interpretation of the meanings of the frequency figures varies from worker to worker. One individual may be quite consistent and accurate according to his method of description, but several different, and seriously different, interpretations may be applied to his results by other workers.

(*b*) The frequency numbers used are not numbers in the mathematical sense, but are rather symbols to stand for words or pictures. The numbers 1–5, for example, do not have an arithmetical relation to one another; 2 is not twice one, and 5 is not five times one. The figures in this scheme are not amenable to the ordinary laws of addition, multiplication, etc., and the methods of mathematics cannot be applied to them. Whether such mathematical treatment is necessary and useful is debatable, and something must be said on this question.

Of late, several workers have adopted the methods of counting mineral grains, instead of estimating their frequencies. Such workers claim that the increased accuracy so obtained is both desirable and necessary, and have pointed out the advisability of indicating the relative frequencies so obtained by percentage figures. Fleet advocates a count of from 500 to 1000, or more, grains as the basis for an accurate statement of mineral composition.[1] The writer can do no more than subscribe to the impartial judgment of Milner, who recognizes that the exigencies of the work in hand will often preclude the possibility of such counting. He is, however, willing to admit that, time available, the counting of mineral grains may lead to more exactness in heavy mineral correlation.[2] Whatever be the worth of such refinement in methods, the important fact remains that counting of mineral grains is coming more into use, and the figures obtained by such counting are being expressed in percentages.[3] This paper is concerned with the question of real and apparent accuracies in such representations, and with the application of statistical methods in correlating by heavy mineral percentages.

The problem presented is one of sampling error. The assumption must first be made that an average sample from the bed or outcrop has been secured, and that this sample has been so treated that the slide examined contains a suite typical of the sediment in question.[4] Let the total number of grains in the slide (heavy or light, as the case may be) be represented by N, and the total number of each individual mineral species be given by Y_1, Y_2, Y_3, etc. Then the particular problem is—what error will be made in the case of each mineral species if some number n, less than N be counted, i.e., if y_1, y_2, y_3, etc. (less than Y_1, Y_2, Y_3, etc.) be counted?

The chance that any grain in the slide will belong to a certain species, Y_1, is Y_1/N, usually called the probability or p. The chance that any grain will not belong to such a category is q, $=1 - Y_1/N$. A simple illustration will make this clear. If a slide of 1000 grains contains 250 grains of zircon, the chance that any random grain will be zircon is $250/1000 = {}^1/_4$. The chance that the grain will not be zircon is $1 - 250/1000 = {}^3/_4$. But since we do not wish to count Y_1 or N, p for our purposes becomes equal to y_1/n, and q to $1 - y_1/n$. As n approaches N the error in partial counting decreases, and it will be shown that n must have a certain value for the accuracy desired.

The probable error (p. e.) of counting n grains divided into y_1, y_2, y_3, etc., number of grains in each mineral species, is, for each species, given by the formula:

$$\text{p. e. (in no. of grains)} = 0.6745\sqrt{npq}.^{5}$$

Let us take a concrete example of the use of this formula.

Consider a slide containing a large number of grains. Suppose that 50 grains are counted, and it is found that 30 are zircon, 10 tourmaline, 5 staurolite, and 5 garnet. What error is made in saying that the slide as a whole contains $30/50 = 60\%$ zircon, $10/50 = 20\%$ tourmaline, etc.? In the case of zircon, the p. e. in grains $= 0.6745\sqrt{50\times3/5\times2/5} = 0.6745\sqrt{12}$ or about 2.3 grains. The error in per cent, then, is $2.3/30 = 7.8\%$. In other words, the zircon of the whole slide is as likely to be 52.2% or 67.8% as 60%.

Now consider the p. e. for garnet in the same case.

$$\text{p. e. (grains)} = 0.6745\sqrt{50\times1/10\times9/10} = 0.6745\sqrt{4.5} = 1.4 \text{ grains.}$$

The p. e. in per cent $= 1.4/5 = 28\%$, i.e., garnet is as likely to be present as 7.2% or 12.8% of the whole slide as it is 10%. From this there comes the simple but not always obvious fact that in a count of n grains, the p. e. of the abundant species will be much lower that the p. e. of the scarce or rare ones. Also for a species having a given frequency, p and q will not vary, and the p. e. will be a function of n—more specifically will vary directly as $\sqrt{n}$. Hence, for each mineral species, with its percentage of frequency in the whole slide, there can be plotted a curve connecting p. e. (p. e. in $\% = \text{p. e.}/y_k$, where y_k = number of grains of any species found in n grains of slide) and n. Figure 1 represents a sketch of six such curves; that marked 5% connects n and p. e. for a species occurring as 5% of count. To the left of this curve are those for mineral species present in higher percentages.

The actual use of such curves would be roughly as follows: first, a count of, say, 100 grains is made. From this count there will be found present, for example, 70% zircon, 10% tourmaline, 10% staurolite and

10% garnet. Following the ordinate 100 on "n" over to the right, extrapolation between the 60 and 80% curves will give an error of about $4^1/_2$% for zircon. In like manner the error of all three 10% species will be 20%, i.e., their percentage is as likely to be 8 or 12% as 10%. Suppose an additional hundred be counted, and in the total of 200 grains, zircon now has a percentage of 80, tourmaline 15, staurolite 10 and

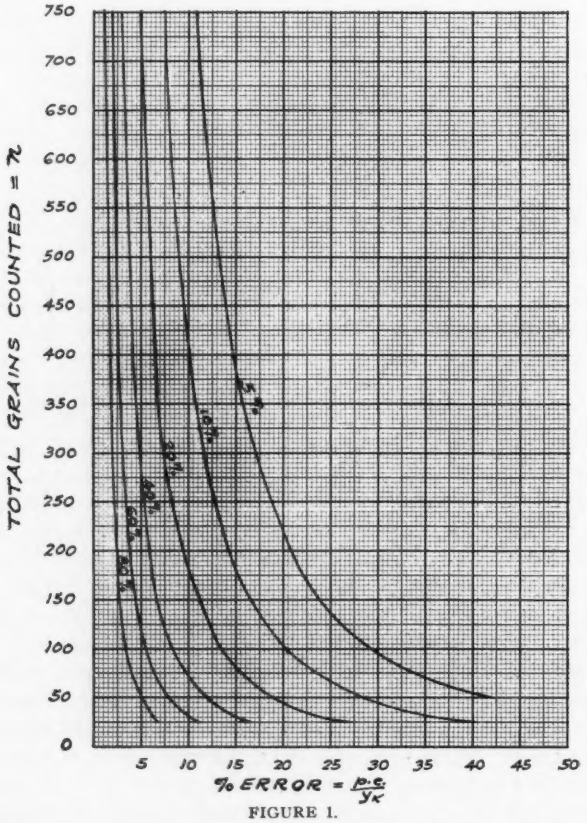

FIGURE 1.

garnet 5. Now the error for zircon is about $2^1/_2$%, for tourmaline about 12%, staurolite 14% and garnet 21%. If 500 grains be counted, and the relative frequencies remain about the same, the respective errors would be about $1^1/_2$, 8, 9 and 13%. Thus, the accuracy increases very slowly after the sharp "bends" of the curves are passed and their nearly straight parts reached, i.e., as n becomes large. In general, the accuracy in-

creases as the $\sqrt{n}$, so that if twice the accuracy is desired, 4 times as many grains must be counted, if 3 times the accuracy, 9 times as many, etc. The "law of diminishing returns" probably will make us content to count but a few hundred grains. Perhaps 300 will suffice for most ordinary work, and even then the accuracy will far transcend that attained by estimation. A word must be said with respect to the presentation of the results so obtained.

The writer wishes to introduce no new or fancy methods for representing the results of heavy mineral analysis. He recognizes that probably the most acceptable method is that already in use, i.e., to indicate the frequency of each species as a percentage of the total counted. He does, however, wish to stress heavily two points:

(*a*) That the worker himself should be cognizant of the errors inherent in the analysis in question, and that he should not indicate an apparent accuracy greater than is genuine. Let us take an example of such apparently great accuracy. W. F. Fleet[6] has given a table of heavy mineral frequencies in a certain sandstone, in which table the percentages are given as accurate to one-tenth of one per cent, in other words, an accuracy of one part in a thousand. Let us calculate the number of grains counted which would give such an accuracy, choosing for this a species which composes about 50% of the sample.

$$\text{p. e.(grains)} = \text{p. e.}/y_k(\%) = 1/10\% = 0.001$$

from the formula $\frac{\text{p. e.}}{y_k} = \frac{0.6745\sqrt{npq}}{y_k}$ (dividing both sides by y_k to get the result in %) we have

$$0.001 = \frac{0.6745\sqrt{n \times 1/2 \times 1/2}}{y_k},$$

but $y_k = n/2$ in this case so

$$0.001 = \frac{0.6745\sqrt{\frac{n}{4}}}{\frac{n}{2}}.$$

Solving this equation we have $n = 454{,}950$.

For an accuracy of 1/10% in a species composing $^1/_2$ the sample the above appalling count is necessary. A count of 4549 is required for 1% accuracy, and about 200 for 5%. In practice it probably will be found that the mineral percentages of samples taken from different localities in the same bed or formation will differ so widely among themselves that determining frequencies of any one sample to much less than 5% error will be a simple waste of time.

To indicate the true accuracy of the result, probably the most logical way would be to indicate the apparent value plus or minus the p. e., for example, 50 ± 13%. It is a bother, however, both to calculate accuracies (without prepared curves) and to indicate them as above. It seems satisfactory to indicate frequencies by simple percentages, if the following and second point be stressed:

(*b*) That the worker be not only cognizant of his own error but that he state definitely his method of arriving at the percentages given and/or append the errors so involved, so that the reader will not be misled into assuming that, for example, 58.1% means 58.1%, when it might as well be 50 or 70%.

The average reader then, will do well to be on his guard in correlations based on apparently accurate percentages. The errors present may permit of doubt in correlation, or may show similarities in groups superficially unlike.

The writer has said little or nothing of the utility of such methods as are outlined above. He believes that the time is not ripe for passing judgment. Correlation by mineral percentages is at present almost untested, and on fair trial alone can it be pronounced useful or without value.

Summary.—There is a growing tendency to increase the accuracy of investigation of the frequencies of minerals in sediments. An apparent increase in accuracy is obtained by representing these frequencies as percentages. In this case, however, it is necessary that both author and reader have full cognizance of the errors inherent in the methods used and, to this end, it is essential that the author give in detail his methods of work, so that the validity of his conclusions can be accepted.

[1] Fleet, W. F., *Geol. Mag.*, **63**, 506, 1926.

[2] Milner, H. B., *Sedim. Petrog.*, pp. 383–386, 1929.

[3] See, for example, papers by Ockerman, *Jour. Geol.*, **38**, 4, and Graham, *Jour. Geol.*, **38**, 8, as well as the paper by Fleet, op. cit.

[4] See paper by C. J. C. Ewing, *Geol. Mag.*, **68**, 1931, pp. 136–140, on variations in results by different methods of separation.

[5] The derivation of this formula may be found in any standard textbook on statistics.

[6] Op. cit., p. 509.

IV. THE METHOD OF ACTION OF PITUITRIN INTRODUCED INTO THE VENTRICLE

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It has been heretofore shown: (1) That the extract of the neurohypophysis (pituitrin) when injected into the cerebral ventricles usually provokes a striking and characteristic reaction; (2) that pilocarpine likewise introduced causes a highly similar response; and (3) that the preliminary administration of atropine, whether given subcutaneously or put into the ventricle, appears completely to inhibit the intraventricular response not only to the extract but to the drug.

Do these substances so introduced act peripherally after resorption into the blood-stream, or do they act directly upon subependymal and diencephalic nerve centers? In the attempt to answer this question it might be assumed, since the substances have always been injected into the lateral ventricle, that they might easily become resorbed into the blood-stream either through the ependyma or by way of the choroid plexuses which lie exposed in the ventricles.

It has been pointed out that this action by resorption is scarcely probable, at least in the case of pituitrin, because when given intramuscularly or injected into the blood-stream its effect is wholly different from that which follows its introduction into the ventricle. In the case of pilocarpine, on the other hand, no such differences in action are apparent, and it might well enough be assumed, since pilocarpine acts quickly by whatever method it is administered, that it is resorbed in some way into the blood-stream and then acts, as pharmacologists assume that it typically acts, on the myoneural junction in the case of smooth muscle and on the peripheral nerve mechanisms in the case of the secretory glands which are affected by it.

In looking for an answer to this query, as propounded, it has been felt that the several patients in whom the intraventricular injections either of pilocarpine or pituitrin have been without effect might give valuable information. The negative responses which have occasionally been observed are divisible in three principal groups: they occur (1) when an insufficient dose has been administered; (2) when the ventricles have been greatly expanded by hydrocephalus; and (3) when the interbrain has been the seat of tumour. These three groups will be separately considered.

(1) *Insufficient Dosage.*—Necessarily, owing to inexperience, the effective dose either of pituitrin or pilocarpine given in the ventricle has

been a matter of guesswork. To establish the smallest dose of any drug that will provoke a characteristic response and the largest dose that can be given with safety is a pharmacological problem difficult enough, because of individual idiosyncrasy, even in normal subjects. Nor has this been the purpose of these studies in which the tests have all been made on patients convalescent from operations for a variety of intracranial disorders. The fact that the responses which have been described occur under any circumstances is surprising enough and we must for the present let it go at that. The main point to be borne in mind is that all of the subjects (apart from those that fall in the groups 2 and 3 to follow) possess, so far as one can judge, normally reacting interbrains unaffected by the disorder for which the operations were done even in the case of the pituitary adenomas which dominate the list.

That a cubic centimeter of "surgical pituitrin" should have been hit upon as a fair average dose was purely fortuitous and even so there is great variability in the responses, from one so mild it might easily escape notice, to one so severe it is humane to check its course by a hypodermic of morphia and atropine. In one instance a cubic centimeter of the weaker "obstetrical pituitrin" failed to cause any discernible reaction whereas the same dose of surgical pituitrin gave a marked response. And in the preceding paper an experience was cited with a patient, almost certainly with a normal ventricular system, whose response to one cubic centimeter of surgical pituitrin was mild whereas the response to 1.5 c. cm. was extreme.

(2) *An Accompanying Hydrocephalus.*—On a few occasions pituitrin has been injected into hydrocephalic ventricles usually though not always with a negative effect. This might be explained in various ways: by the degree of dilution of the extract in the abundant fluid; by the possibility that secondary pathological changes of some sort in the choroid plexuses or ependyma prevent resorption; or (and what seems most probable) by the extreme distension of the third ventricle in whose paper-thin walls the nuclei, on whose stimulation the responses are assumed to depend, have either been destroyed or thrown out of function. The following experience is an example:

Mrs. P., 40 years of age, had suffered for two years from suboccipital headaches with increasingly unsteady gait and recent blurring of vision. Examination showed unmistakable signs of a cerebellar tumour with secondary hydrocephalus and a choked disc advancing to atrophy. At operation, on October 10, 1930, a large median cerebellar astrocytoma was encountered and extirpated intact together with the roof of the widely expanded fourth ventricle.

She made an excellent recovery from the operation and on October 24th an intraventricular injection of 1 c. cm. of surgical pituitrin was given through the burr hole which had been made over the occipital pole to tap the ventricle during the course of the operation. There was no recognizable reaction of any sort. On the following day, October 25th, 2 c.cm. of surgical pituitrin were similarly introduced again with no

determinable symptomatic response apart from a drop in urinary secretion to 400 cc. for the ensuing 24 hours.

It is assumed that in this patient the long-standing extreme dilatation of the ventricles produced by a slowly growing cerebellar tumour, which from the first must have caused some degree of hydrocephalus, had in the course of time left the hypothalamic nuclei unresponsive to the effect of the extract. Whether in such a case, now that the hydrocephalus has been relieved, the damaged hypothalamic nuclei will regain their susceptibility to the direct action of pituitrin is undetermined; but I am inclined to believe that they will.

In another instance a patient with a more acute hydrocephalus secondary to an acoustic tumour showed, after operation, a reaction to 2 c. cm. of pituitrin so marked it was checked after 45 minutes by an injection of atropine, the temperature meanwhile having dropped 2.8°F. Hence in the presence of secondary hydrocephalus a variability in the responses may be expected, depending, one may assume, on the degree of anatomical and functional alteration in the diencephalic nuclei brought about by the ventricular distension.

Still another instance may be cited. A child with a long-standing hydrocephalus of marked degree secondary to a chronic inflammatory process around the brain stem had a marked hyperthermia after the prolonged cerebellar operation undertaken to reëstablish the escape of fluid. A cubic centimeter of pituitrin injected into the ventricle twice a day for several days had an apparent definite effect in lowering the temperature but there were no other appreciable symptoms.

The degree to which the walls of the third ventricle may be thinned out by a chronic hydrocephalus is well known. A typical example is shown in the accompanying photograph (Fig. 1). Histological studies of the paper-thin walls of such a ventricle show the presence of scattered nuclei but the degree of functional impairment is impossible to estimate.

(3) *With Hypothalamic Tumour Involvement.*—In this connection, though there are only two cases to report, and they were not as fully checked as one might now wish they had been, we nevertheless may feel on a little more certain ground than in the foregoing discussion regarding hydrocephalus. The essential details of the more informing of the two cases are as follows:

The patient, a married Russian Jewess, 49 years of age, was admitted to the Medical Service on September 8, 1930, with a history of vomiting and epigastric pain of two weeks' duration. There was a suspicion that she had a carcinoma of the stomach but this was finally ruled out by gastro-intestinal studies. A lumbar puncture disclosed xanthochromic fluid, and curiously enough her brother, whose cerebrospinal fluid had also been found xanthochromic, had died in the hospital several years before with the diagnosis of a cerebral tumour.

She was transferred to the Surgical Service on September 20th at which time examination showed a highly emaciated woman apparently quite unaware of her surroundings and in no seeming pain or distress, but wholly uncoöperative, incontinent, and in a peculiar speechless state of mental negativism. There was constant picking at the bedclothes, a marked clutch reflex, so that it was difficult to disengage her hands from what might be put into them, some exaggeration of the deep reflexes and an apparent stiffness of the neck. A slight, questionable papilloedema was noticed in

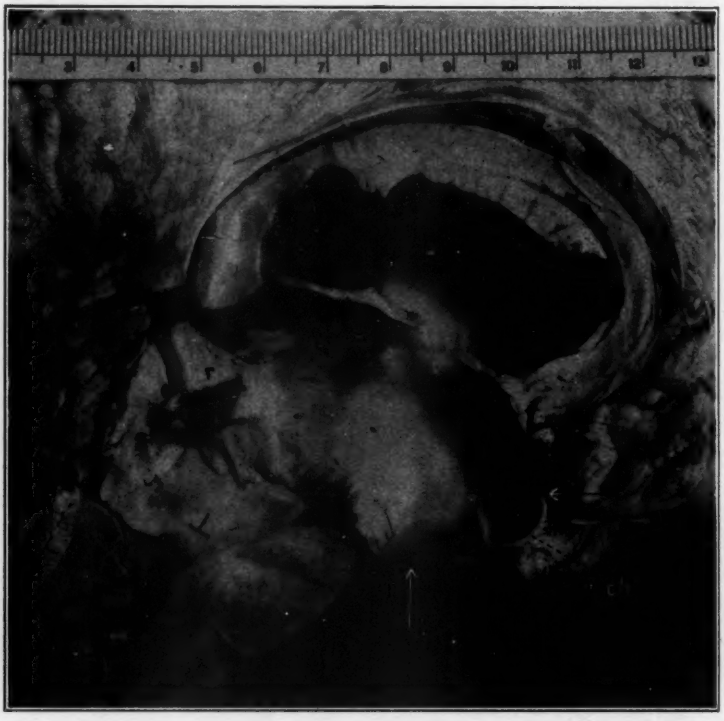

FIGURE 1

Showing (natural size) the extreme degree of expansion of third ventricle in obstructive hydrocephalus due to tumour of the corpora quadrigemina. Note the paper-thin walls of the ventricle above and posterior (arrows) to the chiasm (ch).

the right eye alone. There was pupillary inequality, the right usually being a little larger than the left. The neurological examination was otherwise negative. Her cranial roentgenograms showed no abnormality.

A frontal tumour, possibly metastatic, was suspected. Ventriculograms showed an irregular filling defect involving the anterior part of the third ventricle, with evidence also of a mesial filling defect in the anterior horns of both lateral ventricles, particularly the left (cf. Fig. 3).

On September 24th, a right osteoplastic flap was turned down and a subtemporal decompression made with the expectation that ventricular distension would cause a subsequent bulging of the flap which would facilitate an attack on the tumour at a later time. As a matter of fact, the decompression remained collapsed, there was no subsequent elevation of the flap or other evidence of any increase of intracranial tension up to the time of the patient's death in the hospital four weeks later.

She had been given in the interim a series of x-ray treatments, and on October 11th ventriculography was repeated to see whether the ventricles had dilated and whether there had been any advance in the filling defect caused by the lesion, but no change was demonstrable.

One peculiar thing happened on October 17th, namely, a sudden bilateral oedema of both hands associated with the rapid development of bullae (Fig. 2).

FIGURE 2

Showing the acute oedema with bullae formation in the clutched hand of the patient with tumour destroying the tuber cinereum.

Intraventricular Injections of Pituitrin and Pilocarpine.—Under the belief that the patient's symptoms of "negativism" indicated a destructive lesion of the hypothalamus it was thought justifiable to make a test with intraventricular pituitrin to see whether it would give the customary reaction. Accordingly on October 17th a cubic centimeter of surgical pituitrin was introduced with no determinable change whatsoever in rectal temperature, pulse, or blood-pressure; there was no vomiting or appreciable alteration in the color or degree of moisture of the skin.

A few days later an intraventricular injection of five milligrams of pilocarpine gave no reaction except three explosive attacks of vomiting 10 minutes, 20 minutes and 25 minutes after the injection. No other recognizable effects of the drug whatsoever were detected.

During the next three weeks there was a slow, gradual failure with progressive emaciation in spite of the fact that she took nourishment well. Though apparently conscious,

she never moved other than to hold clutched the bedclothes or whatever might have gotten into her hand; and she never spoke. She was supposed to be hypersomnolent but as she usually kept her eyes open, it was difficult to say most of the time whether she was sleeping or not. There was no evidence at any time of a polydipsia. Owing to incontinence the urine could not be measured. A sudden rise in temperature to 105° on November 17th ushered in the end.

The post-mortem examination was limited to the brain. Coronal sections showed a

FIGURE 3

Showing the subcallosal glioma projecting into and involving the frontal horns of the ventricles. Coronal section at level of chiasm.

median, subcallosal, anteriorly placed glioma (Figs. 3 and 4). The tumour had completely destroyed the septum and had projected into the ventricles. It occupied and wiped out the anterior part of the third ventricle, leaving the foramina of Monro open and the posterior part of the third ventricle intact. There was only a slight dilatation of the lateral ventricles, within which the choroid plexuses appeared normal. A mesial section of the brain showed that a gravitation metastasis from the tumour into the infundibulum had almost completely destroyed the tuberal region (cf. Fig. 5).

This, then, was a case in which pituitrin and pilocarpine introduced into the ventricle failed to have their usual stimulatory effect, presumably owing to the neoplastic destruction of the centers concerned in the normal reaction.

A similar experience, though in the absence of a post-mortem examination somewhat less telling, was had with another Russian woman, 57 years of age, with a tumour of the third ventricle similarly demonstrated by ventriculography. She had progressive

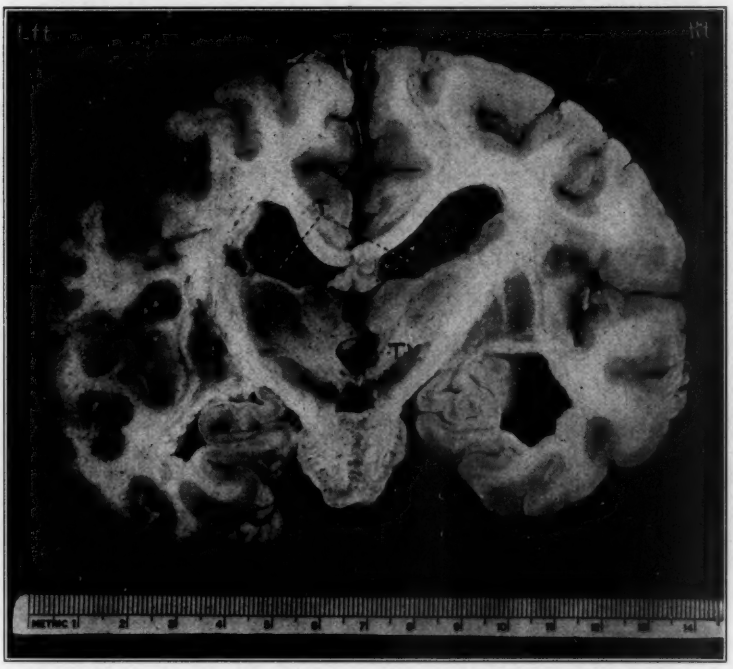

FIGURE 4

Coronal section (cf. Fig. 3) to show from behind the slight dilatation of the lateral ventricles in which tumour (T) can be faintly seen. The posterior portion of the third ventricle (T.V.) remains uninvolved.

symptoms over a period of 12 months, characterized by somnolence, mental deterioration, incontinence, and unsteadiness of gait, which were long ascribed to cerebral arteriosclerosis. In this case there was a moderate choked disc and ventriculograms showed a fairly marked expansion of the lateral ventricles, air passing freely between them, with an upward and forward displacement of the third ventricle as from a suprasellar tumour or a tumour of the ventricle itself.

In this patient also an osteoplastic flap with decompression was made, but here again

no especial evidence of pressure was found nor was there a subsequent tendency for the ventricles to fill or the flap to become elevated.

An intraventricular injection of one cubic centimeter of surgical pituitrin caused no reaction whatsoever except a slight rise in blood-pressure from 110/65 to 140/85 which persisted for the next two hours, accompanied by slight acceleration of the pulse from 65 to 75 over the same period of time. There was no change in temperature, no flushing

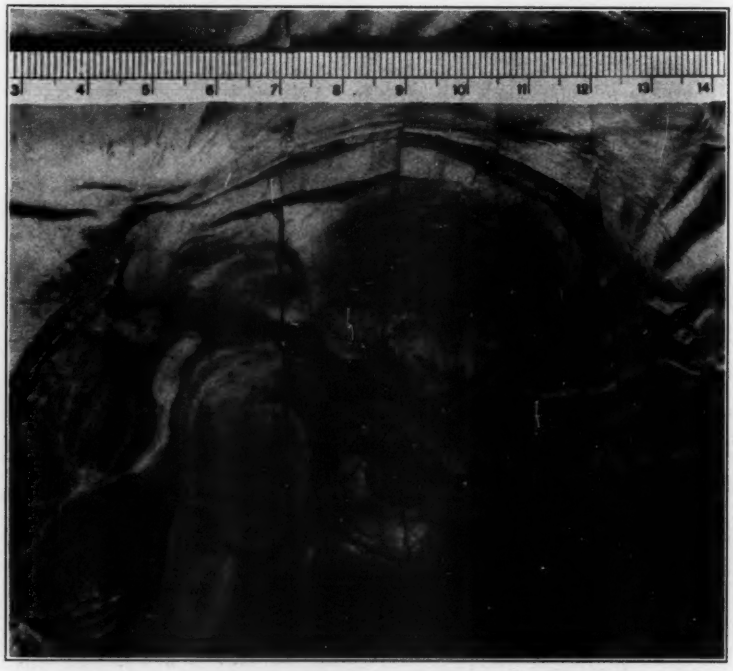

FIGURE 5

Mesial section of brain (natural size) for comparison with figures 3 and 4, showing the situation of the primary tumor with implantation involvement of infundibular cavity and complete destruction of tuber, (Tr) the posterior part of the third ventricle remaining free.

or sweating; a single attack of vomiting with a bowel movement occurred two hours after the injection.

It has been shown by Cannon and his co-workers[1] that an animal may survive after complete removal of its thoraco-lumbar sympathetic chain of ganglia. Similarly, it would appear that in man life may be maintained after apparent destruction of the diencephalic centers for parasympathetic action. It has been found possible on two occasions to remove extensive

tumours (ependymomas) from the third ventricle, the walls of which must have been seriously damaged in the process. Recovery in each instance nevertheless took place and the patients continue to lead essentially normal lives. It would appear, therefore, that complete paralysis of either sympathetic or parasympathetic system is less serious in its effects than abnormal or perverted stimulatory disorders affecting either system.

In contrast to these supposedly paralytic pathological conditions affecting the interbrain and which we have herein described, one may occasionally encounter irritative ones which cause stimulatory responses on the part of the autonomic system. No better example of this has appeared in the literature than that reported by Penfield[2] of what he calls diencephalic autonomic epilepsy. The case was that of a middle-aged woman who had a small cholesteatoma of the third ventricle which supposedly caused periodical irritation of the adjacent hypothalamus provoking peculiar seizures characterized by sudden sweating, flushing, salivation, lachrymation, hiccoughing, respiratory disturbances and fall in temperature which were regarded as evidences of autonomic stimulation. That they were essentially parasympathetic phenomena and, apart from the absence of vomiting, fully comparable to those which the intraventricular injection of a cubic centimeter of pituitrin produces is quite obvious.

Conclusions.—Negative responses to the intraventricular injection of pituitrin may occur naturally enough when the dose is insufficient and there may of course be individual variations in susceptibility to its effects. The customary responses may also fail to occur when a marked degree of hydrocephalus serves to balloon the walls of the third ventricle and also when the ventricular walls are involved by a tumour. Both of these conditions presumably serve to throw out of action the hypothalamic nuclei whose stimulation is assumed to call forth the typical reaction.

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V. THE COUNTERACTIVE EFFECT OF TRIBROMETHANOL (AVERTIN)* ON THE STIMULATORY RESPONSE TO PITUITRIN INJECTED IN THE VENTRICLE

BY HARVEY CUSHING

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In the foregoing discussion of the method and place of action of pituitrin and pilocarpine when put into the ventricle, one of the arguments favoring the stimulation of hypothalamic nuclei was based on the negative responses shown by patients with pathological lesions involving the interbrain (tumour and hydrocephalus). Interpretations of physiological responses in the normal subject are difficult enough, and to bolster an argument by the absence of responses in pathological states, however suggestive they may be, is unconvincing.

Were there some certain method of experimentally inhibiting the diencephalic centers before the injections were made, their locus of action might be more definitely determined. The preliminary injection of atropine, to be sure, has been shown to be counteractive but the known antidotal effect of atropine on pilocarpine, however given, and its apparent antidotal effect on pituitrin intraventricularly administered serves possibly to exclude it from consideration. Procaine ("novocaine") immediately suggests itself but its effect as a respiratory depressant when injected into the ventricles of animals precludes its employment in man on the ground of unjustifiable risk, though the drug is employed daily for abdominal operations or even for operations on the chest and neck after its subarachnoid injection by the lumbar route.

To these objections of undue risk the narcotics are reasonably free though there is no unanimity among pharmacologists as to how and where hypnotics of various kinds act in the production of unconsciousness or sleep. Those who have studied the effects of cortical stimulation, whether experimentally on laboratory animals or for purposes of delimiting the motor cortex during the course of operations on the brain of man, have long known that, when the subject is under deep inhalation narcosis from ether or chloroform, cortical responses are not obtainable. Not until the twilight stage of awakening from the effects of the anaesthetic is reached does the motor cortex regain its electrical excitability.

The barbituric acid derivatives, of which several are employed for the production of surgical narcosis, are generally assumed to exercise their effect on the interbrain. Into one of these substances known as diallyl

* This commercial product is a combination of tribromethyl alcohol dissolved in amylene hydrate customarily given in a dose of one hundred milligrams per kilogram body weight.

barbituric acid ("dial-ciba"), E. and J. Keeser[1] succeeded in introducing an iron group without altering the anaesthetic property of the compound; and after it had been administered and the animal kept under its influence for several hours and then killed by bleeding, a Prussian blue reaction showed that the drug was chiefly concentrated in the thalamic and hypothalamic regions. In view of this, it is highly interesting that Fulton, Liddell and Rioch[2] have recently found that "dial" administered to monkeys in amounts sufficient to produce deep surgical anaesthesia leaves the electrical excitability of the cortex unimpaired, and they assume consequently that its locus of action is chiefly on sub-cortical centers, i.e., thalamus, hypothalamus, midbrain and upper medulla.

Tribromethanol (avertin), though a narcotic chemically unrelated to the barbituric acid combinations, nevertheless appears to act in precisely the same way on man that Fulton, Liddell and Rioch found "dial" to act in the ape insofar as it fails to diminish the electrical excitability of the cortex in the way that ether and chloroform do. This can be personally vouched for by the following experience:

A doctor's son had been victimized by repeated attacks of Jacksonian epilepsy invariably beginning in the right hand and occasionally passing on to unconsciousness. An osteoplastic exploration of the left hemisphere was made in the hope of finding a focal lesion that might be surgically dealt with, or, in its absence, with the intent of extirpating the pre-Rolandic hand-area. The operation was begun under local anaesthesia but the boy was so restless and uncoöperative that avertin was given per rectum, and he quickly passed into the usual profound sleep. The cortex when exposed was found hyperaemic but otherwise normal. Though the pre-central area for the upper extremity was fairly evident, to exclude any possible topographical error the cortex was stimulated by the unipolar method with a faradic current barely strong enough to cause contraction of a bundle of exposed temporal muscle. The area for the hand was thus certified, the motor responses in thumb and fingers being as sharp and easily elicited as if no anaesthetic had been used.

My personal familiarity with the barbital compounds as anaesthetics has been negligible, but tribromethanol has come to be used with sufficient frequency in the clinic so that we have a fairly definite understanding of its physiological reactions other than that producing unconsciousness. Sleep ordinarily comes on with surprising promptitude, a few minutes after the drug has been introduced into the rectum. At the same time an extreme contraction of the pupils occurs, soon followed by: (1) a definite fall in blood-pressure often as much as 30 to 50 points; (2) a slight rise in pulse in certain cases amounting to 20 to 30 beats; (3) some slight increase in respiratory rate; and (4) a slight fall in body temperature of 1 to 2 degrees. At the end of 60 to 90 minutes there is usually a fairly abrupt termination of these reactions though fluctuation in size of the pupils and in the depth of the somnolence may persist for varying lengths

of time. We have also observed a drop in blood-sugar, a considerable diminution in the erythrocyte count, and other minor changes which scarcely deserve mention as the data regarding them are insufficient.

The most striking effects of the drug are three: the *deep, apparently natural sleep*, the *pupillary contraction*, and the *fall in blood-pressure*. If these are actually central and diencephalic in origin, the hypnosis may be accounted for on the basis of stimulation of the "sleep center" assumed on experimental grounds (Hess) as well as on clinico-pathological ones (postencephalitic hypersomnia) to lie somewhere in the interbrain. It has no apparent relation to the autonomic nervous system.

Pupillary reactions, on the other hand, supposedly have such a relation and the disclosure by Karplus and Kreidl[3] that electrical stimulation of the lateral wall of the hypothalamus causes dilatation of the pupils was what first led to the belief that there must be a higher "sympathetic center" in the interbrain. Just how one is to explain the prolonged fall in blood-pressure and the drop in erythrocytes unless by an expansion of the spleen is not clear, but it is at least evident that the reaction is the reverse of that which customarily follows the injection of pituitrin and pilocarpine in the ventricles. What is more, the most notable difference between the hypnotic state produced by avertin and the narcosis due to ether or chloroform is the absence of any subsequent vagal effect from the former, postanaesthetic vomiting being most unusual. This, again, runs counter to what we have found to occur after the intraventricular injection of pituitrin, the presumably vagal effect of which in the production of repeated retching and vomiting is striking. Another contrast lies in the dryness of the skin and mouth under avertin and the sweating and salivation that follow the intraventricular injection of the extract.

All things considered then, tribromethanol (should it really act on the hypothalamus when given rectally) and pituitrin (should it similarly thus act when given intraventricularly) are so definitely opposed in their effects one would expect them to be antidotal. The truth of this conjecture appears to be substantiated by the experiences cited in the following two protocols, A and B:

PROTOCOL A. (1) *A typical reaction to* 1 *c. cm. surgical pituitrin injected in the ventricle.* (2) *No reaction to the same injection with the patient under avertin.* (3) *A typical reaction to* 2.5 *mgm. pilocarpine in the ventricle.*

The patient, a man 53 years of age, was satisfactorily convalescing from an operation performed Dec. 2, 1930, for a glioma of the temporal lobe which had not served to cause hydrocephalus. At the time of the test he was wholly free from symptoms relating either to the lesion or his operation.

On December 18, 1930, after the usual preliminaries, at 10.03 A.M., 1 c. cm. of pituitrin was introduced into the ventricle with prompt moderate cutaneous flush, sweating, and salivation, but with only a slight fall in rectal temperature of less than one degree. The most striking effect, though it was unusually delayed, was the vomiting which set

in suddenly about an hour after the injection and which, accompanied by hiccoughing, continued off and on for the next three hours. It was estimated that he must have vomited 500 c. cm. of gastric secretion. This at first was clear, serous fluid but subsequently contained thick, tenacious mucous, finally became bile-stained and had a normal gastric acidity. The frothy character of the secretions suggested some hypersecretion from the lungs but no rales were heard on auscultation.

The erythrocytes, which before the pituitrin injection numbered 4,040,000, were counted 90 minutes later at 4,300,000; and at the end of $3^1/_2$ hours they were 4,170,000 The temperature began to drop in 35 minutes but fell only 1.1° and the basal metabolic rate remained unaffected. Blood-sugar before and after the injection showed no essential change. There was the usual slight rise in blood-pressure from 110/60 to 130/80 which endured for three hours together with a slight increase in pulse rate instead of the customary slowing.

The vomiting had been so persistent and disturbing that at 1.40 P.M. it was checked by a hypodermic injection of 0.5 mgm. of atropine with 5 mgm. of morphia.

This patient, then, showed to intraventricular pituitrin a definite reaction in which retching and vomiting were unusually pronounced. The type of reaction therefore was eminently suitable for a test to determine whether it would be abolished or modified by avertin anaesthesia.

Accordingly, on December 23rd, after the usual preliminaries with the patient fasting, the standard dose of avertin per kilogram body weight was slowly introduced per rectum at 9.35 A.M. with an almost immediate profound sleep, a fall in blood-pressure from 130/70 to 80/60, immediate contraction of the pupils to pinpoint size, increase in pulse rate from 90 to 120, an increase in respiration from 20 to 30. These characteristic reactions were practically over at the expiration of an hour and forty minutes by which time the patient had begun to show some signs of returning consciousness.

At 11.30 A.M., two hours after the avertin administration, 1 c. cm. of pituitrin was put into the ventricle and so far as could be seen this had not the slightest effect. The skin and mucous membrane remained dry. The rectal temperature, which under avertin had dropped from 99° to 96.2°, had begun to rise at 10.50 A. M. and the curve was not affected by the injection of pituitrin forty minutes later. An insignificant fall in blood-sugar was detected when the temperature was at its lowest. The erythrocyte count remained constant within limits of error. *The excessive bouts of retching and vomiting, which had previously been produced by intraventricular pituitrin when given independently, were completely counteracted by the action of avertin.*

Three days later, on December 26th, an intraventricular injection of 2 mgm. of pilocarpine, without preceding avertin narcosis, produced a typical reaction very similar to that caused by pituitrin alone.

The counteractive effect of avertin in the second case to follow was even more striking in that 1.5 c. cm. of surgical pituitrin was injected, an amount of the extract which from a previous experience with the same patient had given an excessive reaction as related in an earlier paper in the series (No. II) in which the effects of intraventricular pilocarpine and pituitrin were contrasted.

PROTOCOL B. *A severe reaction to 1.5 c. cm. intraventricular pituitrin. Under avertin hypnosis the reaction to the same dose of the extract almost completely counteracted.*

The patient, a man 58 years of age, convalescent from an operation for the removal of a temporal glioma and at the time of the tests free from symptoms, had been found to give a typical but mild reaction to 1 c. cm. of surgical pituitrin and a severe reaction to 2.5 mgm. of pilocarpine. Consequently, the better to contrast the effect of the drug and the extract, he was then given 1.5 c. cm. of surgical pituitrin in the ventricles with the results recorded in another connection, viz., prompt flushing, sweating, salivation, lachrymation, retching and vomiting, rise in blood-pressure, slowing of pulse, and a drop of 6°F. in body temperature accompanied by an astonishing rise in metabolism of +43 per cent associated with shivering.

The effect of avertin on this patient was known from two previous experiences. The drug caused a prompt and deep hypnosis, marked pupillary contraction, a drop in the erythrocytes of 400,000, and a fall in blood-pressure from 110/70 to 70/40 with fairly abrupt return to normal on first signs of awaking at the expiration of 90 minutes.

On March 5, 1931, after the usual preliminaries, 6.9 c. cm. of avertin in 280 c.cm. of water were introduced into the rectum at 10.12 A.M. Within 10 minutes the pupils had contracted to pinpoints and he was in a profound sleep. By 10.35 the blood-pressure had fallen from 135/80 to 90/65 and the erythrocytes had dropped from 5,650,000 to 5,080,000. The rectal temperature remained level at 98°F. The skin was warm and dry. At 10.42 A.M. the ventricle was tapped and 1.5 c. cm. of surgical pituitrin was introduced. This had no apparent effect whatsoever. At 11.37 the patient began to arouse, the pupils dilated, and he asked for a drink of water.

At 11.45 he was sufficiently awake to respond to commands and the blood-pressure had begun to rise, 110/70. At this time, 93 minutes after the avertin was given and 63 minutes after the pituitrin was injected, the previously dry mucous membrane of the mouth began to show some moisture and visible beads of perspiration appeared on the skin. This mild reaction lasted for 45 minutes before it had wholly disappeared. Meanwhile the temperature dropped from 98° to 96.4°. At 12.50 when the temperature was at its lowest level, the metabolism which at the outset was zero was found to be −2, in other words, it was unchanged within the limit of error. There was no nausea or vomiting or discomfort of any kind and on returning to the ward the patient took his dinner with appetite.

In the first of these cases, therefore, avertin served completely to offset the patient's known reaction to one cubic centimeter of intraventricular pituitrin (vomiting, retching, salivation, flushing, sweating, rise in blood-pressure, etc.) when given by itself. In the second case, the larger dose of 1.5 c. cm., which had at a previous session caused a severe reaction with an unusually marked fall in temperature, gave evidence of a trifling and much delayed pituitrin effect shown by transient sweating and a slight fall in temperature after the inhibitory influence of the avertin had begun to wear away.

It can be seen that the pharmacological action on hypothalamic centers of intraventricular pituitrin and of avertin is definitely antagonistic. The chief discord lies in the pupillary contraction under the blood-borne avertin and the absence of any notable pupillary effect from pituitrin which is assumed to act by diffusion through the ependyma. This, however, may well be accounted for on the grounds that the pupillary center lies too deep to be acted upon by resorption, and it may be noted

that no pupillary dilatation was observed when atropin was injected into the ventricle. In the recent experiments of Karplus and Peczenik[4] previously referred to, it was shown that in the cat electrical stimulation of the tuber cinereum does not cause enlargement of the pupil but that it occurs only when the outer walls of the hypothalamus itself are stimulated. Stimulation at either point nevertheless apparently serves to discharge the posterior lobe and thereby to increase the oxytocic and melanophore-expanding properties of the cerebrospinal fluid.

Conclusion.—The hypnotic tribromethanol (avertin) presumably causes its effects by action on centers in the diencephalon, and serves to counteract the stimulatory responses to pituitrin injected into the ventricles.

[1] Keeser, E. and J., "Uber die Lokalisation des Veronals, der Phenyläthyl- und Diallylbarbitursäure im Gehirn," *Arch. exper. Path. Pharmak.*, 1927, **125**, 251–256.

[2] Fulton, J. F., and E. G. T. Liddell and D. M. Rioch, " 'Dial' as a Surgical Anaesthetic for Neurological Operations, with Observations on the Nature of Its Action," *J. Pharmacol. Exper. Therap.*, 1930, **40**, 423–432.

[3] Karplus, I. P., and A. Kreidl, "Gehirn und Sympathicus," *Arch. ges. Physiol.*, 1909, **129**, 138–144,; *Ibid.*, 1910, **135**, 401–406,; *Ibid.*, 1911, **143**, 109–127.

[4] Karplus, I. P., and O. Peczenik, "Über die Beeniflussung der Hypophysentätigkeit durch die Erregung des Hypothalamus," *Arch. ges. Physiol.*, **225**, 654–669, 1930.

VI. CONCERNING A POSSIBLE "PARASYMPATHETIC CENTER" IN THE DIENCEPHALON

BY HARVEY CUSHING

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In this series of papers it has been shown:

(1) That the injection of commercial pituitrin into the cerebral ventricles produces a prompt and characteristic reaction presumably stimulatory in character; (2) that pilocarpine similarly introduced gives a wholly comparable response; (3) that an antecedent subcutaneous or intraventricular injection of atropine counteracts the action both of the extract and of the drug; (4) that the effector responses do not occur in the presence of lesions which either have destroyed or which appear to have impaired the functional activity of the interbrain, more particularly its hypothalamo-tuberal portion; and (5) that with patients under the influence of tribromethanol, a narcotic which presumably acts upon diencephalic centers, intraventricular pituitrin has either no effect or one which is slight and much delayed.

While the clinical tests which have been described have been under way, efforts have been made to supplement and check them by corresponding observations in the experimental laboratory. Though there is no belittling the greater difficulty both of carrying out and of interpreting similar pharmacological tests conducted on the lower animals, some

progress has nevertheless been made by my junior co-workers, Drs. Light, Lawrence, Dial, Boyes and Strayer, who will have some reports of their own to make on the subject. It may suffice at this time to say that the responses to intravenous and to intraventricular pituitrin in the dog are similar to those seen in man. The intravenous injection causes, as others have shown,[1] what appears to be chiefly a sympathetic effect, namely, an extreme pallor of skin and mucous membrane with contraction of the spleen from a vascular rather than capsular constriction. The intraventricular injection on the other hand causes a wholly different and apparently a parasympathetic reaction, namely, vascular dilatation, excessive panting, salivation, signs of pulmonary oedema and gastro-intestinal hypertonicity.

Corresponding studies on primates have been made by J. F. Fulton and his co-workers in the Physiological Laboratory at Yale; and I am permitted to state that they find the intraventricular injection of pituitrin in monkeys to have an effect corresponding in a general way to that which occurs in man, though no comparable antipyretic reactions have been observed. Much labor necessarily lies ahead before the finer details of the responses can be thoroughly worked out.

In our own experimental laboratory chief attention has been paid to the effects of the injections on splenic contracture, on blood fat, and so on, which have required repetitions of observations scarcely justifiable on patients in the clinic, however willing they may be. Dr. Light, moreover, has shown that pilocarpine put in the ventricles of rabbits will cause gastric ulcers in a much smaller dose than Underhill and Freiheit[2] found necessary to produce the same effects when the drug was given subcutaneously.

In seeking to correlate and explain these observations both on man and animals, it has been assumed that pituitrin and pilocarpine are capable of stimulating hypothalamic nuclei which preside over important so-called vegetative functions. And since many of the responses like vaso-dilatation, sweating, salivation, lachrymation, and gastric hypersecretion with retching and vomiting are suggestive of a parasympathetic effect, the existence of a "parasympathetic center" in the interbrain has naturally been postulated.

For a surgeon to suggest an interpretation of matters so complicated and so far removed from his legitimate field would savour of impudence were it not that the surgery of the autonomic nervous system, though still in its infancy, has made rapid strides since the periarterial sympathectomy of Leriche and Royle's operation of ramisection came into vogue. And even should the interpretation of the effects, that have been observed to follow the intraventricular injections as described, prove to be wrong, it may, like the ardently combated views of Hunter and Royle, be pro-

vocative of new investigations of old problems, not without profit; and the neurosurgeon unquestionably will come to take part in them.

Historical Review.—The largely unmyelinated neurones composing the autonomic (Langley) or vegetative (Meyer) nervous system, all agree, play upon structures and organs that are wholly or in large part automatically controlled. Based chiefly on the discovery of the preganglionic relay of fibres to the paravertebral chain of ganglia, the involuntary nervous system has come to be divided into two structurally distinguishable divisions: namely, the sympathetic or thoraco-lumbar division which serves to separate the more headward or cranial and the more caudal or sacral divisions. These cranial and sacral divisions, which have been found to act more or less in definite opposition to the thoraco-lumbar or sympathetic division, have been variously designated, but Langley's term "parasympathetic" has come to be commonly employed for them.

Known by whatever name, these three divisions of the autonomic system, unlike the sensori-motor apparatus, which up to the time of Gaskell, Langley and Anderson had largely dominated neurophysiological research, supposedly act upon the glandular structures and smooth muscle of the blood-vessels and viscera through involuntary automatic reflex arcs. The reflex centers for the preganglionic sympathetic fibres came to be anatomically identified in the lateral horn of the gray matter of the cord, whereas those for the cranial autonomic were experimentally located somewhere in midbrain and medulla.

But however independent of volition and the cerebral cortex these divisions of the autonomic system may be, ever since Karplus and Kreidl[3] found in 1909 that electrical stimulation of the hypothalamus (*Zwischenhirnbasis*) gave a sympathetic effect in dilatating the pupils, contracting blood-vessels, and accelerating secretions, there has been a growing tendency among physiologists to accept the probability of a higher center at least for the sympathetic division of the system. The Vienna school, indeed, has been largely responsible for the promulgation of this idea to which not only Karplus and Kreidl, but Ascher and Erdheim contributed in their attribution of presupposed pituitary symptoms to lesions of the hypothalamus or tuber. The matter was soon taken up from a pharmacological standpoint by Hans Horst Meyer[4] (1912) who with Gottlieb in the successive editions of their "Experimentelle Pharmakologie" have accepted the existence of special higher centers for parasympathetic as well as sympathetic systems, both of which are specifically acted on by drugs.

Whereas adrenalin supposedly acts on the sympathetic nerve endings in precisely the same manner as does a general sympathetic stimulation, the effect of poisons of the pilocarpine group, which are effectively counter-

acted by atropine, corresponds in the opinion of Meyer and Gottlieb to a parasympathetic stimulation. They, however, are obliged to admit that the striking effect of these poisons in the cutaneous glands has not as yet been proved to be wholly parasympathetic though, this exception to the general rule of opposite action of sympathetic and parasympathetic stimulation is, they believe, only an apparent one which will come to be explained by further investigation of the method of innervation.

Though the opportunity of testing the intraventricular action of drugs that influence one or another division of the autonomic nervous system has not been grasped by pharmacologists, Meyer and Gottlieb make certain statements that are highly pertinent to the subject at hand. They state for example (loc. cit., IV. Auflage, page 158), that irritation of the sympathetic system increases metabolism and body temperature whereas the parasympathetic system appears—without its being possible as yet precisely to prove the matter—to lead to the opposite effect. Since a similar pharmacological reaction implies a similar chemical structure, all sympathetic end organs must be chemically alike and all parasympathetic ones equally so. And in illustration of this pharmacological law they point out that picrotoxin, for example, stimulates the parasympathetic system throughout "sometimes not only in the end organs but centrally" and that tetrahydro-β-naphthylamin similarly excites both centrally and peripherally the sympathetic (thoraco-lumbar) apparatus. Whether by "centrally" the authors mean anything higher than the brain stem is not clear, but they may well enough have had the diencephalon in mind.

From the physiologist's point of view, no one in later years has given a more vivid account than Cannon[5] of the manner of action of the autonomic nervous system, more particularly of its intermediary thoraco-lumbar division. In his more recent papers in which the general features of his many contributions have been summarized, he chooses to introduce these new terms: "exterofective" for the voluntary sensori-motor nervous system, and "interofective" for the involuntary or autonomic system. The chief function of this latter system, through its action chiefly on smooth muscle and glands, is to preserve stability ("homeostasis") of the internal economy. Cannon particularly stresses the importance of the thoraco-lumbar division of this interofective system, for through its ability to mobilize the body reserves it may properly be regarded as the special and immediate agency of homeostasis. He emphasizes, too, that the principal effect of the morphological arrangement of relayed neurones in the thoraco-lumbar region is to make possible a diffuse discharge of nerve impulses which constrict blood-vessels, inhibit the activity of the digestive canal, etc., and at the same time lead to a discharge of adrenalin, the hormone and the nervous impulses working together as a sympathico-adrenal system to produce throughout the organism widespread changes

in smooth muscle and glands which are largely defensive in their purport.

Now at the same time it is recognized that the cranial and sacral or parasympathetic divisions of this interofective or autonomic system work more or less in antagonism to the sympathetic (thoraco-lumbar) division. Thus, to give some familiar examples, stimulation of the sympathetic inhibits the muscular tone of the stomach, stimulation of the vagus, which is part of the cranial parasympathetic, increases it; stimulation of the sympathetic dilates the pupil, of the parasympathetic fibres in the oculomotorius contracts it, etc. But this principle of antagonism in the two systems begins to be somewhat less definite in the matter of vaso-constriction and vaso-dilatation; and when we come to the question of sweating, the rule of opposite action appears to have entirely fallen down.

Still another difference in the two systems, as emphasized by Cannon, lies in the fact that the parasympathetic fibres are anatomically so distributed as to favor more or less independent or discriminating activities in contrast to the diffuse action of the sympathico-adrenal system. This is shown in the contraction of the pupils by light, in salivation at the sight of food, in lachrymation, in gastric secretion, and so on, all of these reactions occurring normally quite independently of one another. But this, it seems to me, may merely be a question of strength of stimulus, for the effects we have observed from the injection of pituitrin into the ventricle indicate an apparent diffuse discharge of the parasympathetic system (at least of its cranial portion) as definite as the diffuse discharge of the thoraco-lumbar system which has been the chief object of Cannon's studies.

In thus assuming that the retching and vomiting, salivation, lachrymation, vaso-dilatation and sweating, as well as the effect on the metabolism of water and of fat and also the extraordinary loss of body heat called out by intraventricular pituitrin, represent a diffuse parasympathetic discharge, the posterior lobe hormone may be looked upon as playing by central action very much the same rôle that adrenalin plays by peripheral action in prolonging and intensifying the diffuse discharge of the sympathetic division. Of the two systems, indeed, the parasympathetic, in view of its evident close relation to diencephalo-hypophysial mechanisms, would seem to be far the more important. But this would be difficult to prove, for the cranial autonomic system does not lend itself to experimental extirpation as does the thoraco-lumbar division, the complete removal of which has been so brilliantly accomplished by Cannon[6] and his associates with the surprising disclosure that completely sympathectomized animals may survive for an indefinite time if protected from undue exposure to cold and rendered exempt from the stresses and strains which the struggle for existence would ordinarily call for.

In spite of Cannon's emphasis on the peripheral sympathico-adrenal apparatus, he at the same time has done more than any other to show how it is influenced centrally by primitive emotions; and his studies,[7] supplemented by those of his pupil, Philip Bard,[8] on what they call "sham rage" in decorticated animals, have served to prove the existence of an emotional center in the diencephalon which ordinarily is under some inhibitory influence by the frontal cortex. And it was subsequently shown by Fulton and Ingraham[9] that chronic states reminiscent of "sham rage" could be produced in animals by experimental severance of the fibres that pass to the interbrain from the cortical centers.

In short, emotions such as pain, fear, rage, or a strong excitement of any kind instantly abolish the secretion of saliva, of gastric juice, of pancreatic juice, and of bile, the action apparently (if Cannon is rightly understood) occurring through central stimulation of the sympathico-adrenal (thoraco-lumbar) apparatus. But it would appear that an equally strong case might be presented in favor of the inhibition of the parasympathetic apparatus by these emotional states if a center for this apparatus in the interbrain has any basis in fact.

Since pituitrin when given subcutaneously or intravenously appears to act much like adrenalin as a vaso-constrictor, whereas its effects when put into the ventricle appear to be parasympathetic, it is not unlikely that the posterior lobe hormone may exercise a far greater influence on the three divisions of the autonomic system than has been heretofore suspected. It is possible, too, that its cleavage products, vasopressin (pitressin) and oxytocin (pitocin) isolated by Kamm and his co-workers[10] may not act in the ventricle but only peripherally; and further tests in this direction may throw light on the controversial theories of unitary *versus* multiple hormones for the posterior pituitary.[11]

The Antipyretic, Vaso-dilator and Diaphoretic Effects.—Since the lowering of body temperature, vaso-dilatation and diaphoresis are the three most striking phenomena of the intraventricular-pituitrin reaction, they may deserve brief separate consideration.

The Antipyretic Effects.—Forty years ago, Ott[12] first briefly stated that punctures of the tuber cinereum in rabbits or cats served to stimulate what he called a "thermolytic center," and since that time the possible existence of a heat center or centers at the base of the brain has been investigated by many others who have used a variety of experimental methods. It was found by Isenschmid and Schnitzler[13] that after bilateral removal of the forebrain, of the cerebral hemispheres, striatum and most of the thalamus, a rabbit is still capable of normal heat regulation; but this capacity, once the tuber cinereum is excluded, wholly disappears. Experimental cooling or warming of the region by altering the temperature of the arterial blood-vessels, carotid and vertebral, which supply it (Kahn) or by artificially

cooling or warming the region by direct irrigation (Barbour) have been shown to have marked effects on the thermoregulatory mechanism. Hans Meyer, indeed, has postulated the existence of a "heating" as well as a "cooling" center which, though opposed in action, work hand in hand as a regulating apparatus, fever toxins for example acting on the one, antipyretics acting on the other. What is more, it is appreciated that these centers not only lie in the interbrain but send impulses through the autonomic nervous system; and Meyer goes so far as to say that the *Wärmcentrum* acts through the sympathetic and that the *Kühlcentrum* acts through the parasympathetic. Whether or not this hypothesis is actually open to proof, it at least offers an explanation of the extraordinary antipyretic effect of intraventricular pituitrin which accords with the other responses that are interpreted as being definitely parasympathetic in character.

Barbour and his co-workers have called attention to the fact that heating the carotid blood and cooling the vertebral blood have very similar effects; and they believe that they have shown thereby the existence of two functionally opposed nervous fields, the cooling center being located in the hypothalamic center, the heating center in the medullo-pontine region.

Though the "centers" which govern shivering, at least in the rabbit, have been shown by Dworkin[14] to be rather diffuse, he regards them as an integral part of the heat-regulating mechanism and believes that they are coördinated for service by a superior presiding center in the interbrain. Shivering has only been observed after one of the many tests with intraventricular injection of pituitrin or pilocarpine even when there was a marked fall in temperature, this particular reaction having occurred in a patient who showed, contrary to the usual rule, a marked increase rather than the usual decrease in basal metabolic rate. Apart from this particular case, there has been no exception to the rule that intraventricular pituitrin when it has an effect at all marked either inhibits the mechanisms involved in heat production or, what is more probable, stimulates those involved in heat loss, and these latter are regarded as predominantly parasympathetic in nature.

Stimulation of the sympathetic (thoraco-lumbar) system is known to increase body temperature and Cannon has shown that animals experimentally deprived of this apparatus are prone to lose heat on exposure to cold. What is more, when excited, sympathectomized animals have a tendency to lose heat—an antipyretic effect which might conceivably be explained on the basis of stimulation of an unopposed and still intact parasympathetic apparatus.

Vaso-dilation and Sweating.—In the subjects whose responses to intraventricular pituitrin and pilocarpine have been described, the extremities

have been warm to the touch and the patients have felt subjectively warm even when their rectal temperature has been at its lowest. Conversely, patients with hyperthermia, such as occurs after certain intracranial operations, may have a rectal temperature of 106°F. even though their extremities possess a death-like coldness and clamminess to the touch. Though this, from the standpoint of sweating, sounds somewhat confusing and contradictory, it is safe to say that vaso-dilatation, sweating and the regulation of body temperature are closely related processes even though opinions concerning them, which are almost entirely built up from observations on lower animals, are highly controversial.

Vaso-constriction being admittedly the outstanding effect of sympathico-adrenal stimulation, one would assume on the principle of functional antagonism between the sympathetic and parasympathetic systems that vaso-dilatation would be the normal response to parasympathetic stimulation. But the relation of sweating to these two parts of the involuntary nervous system is highly obscure, it being generally believed by physiologists and clinicians that the sweat glands—at least those of the face and neck—can be activated by either of the opposed divisions.

The pharmacological effects of muscarine, histamine, pilocarpine physostigmine and acetylcholine when given systemically are essentially sudorific and vaso-dilator, and to these better known diaphoretic drugs intraventricular pituitrin must now be added. Though the intraventricular effect of the other substances remains to be studied, pilocarpine at least, as has been made clear, causes generalized flushing and sweating together with a more marked fall in body temperature than could well be accounted for by the effect of evaporation alone.

Sweating and vaso-dilatation, though they customarily go hand in hand, do not necessarily do so, and they have usually been studied independently of one another. Since 1876 when Ostroumoff and Luchsinger showed that faradic stimulation of the severed sciatic nerve could produce sweating in an amputated cat's leg or in one whose circulation was shut off by ligation of the abdominal aorta, the foot-pads of the cat have been the locus, favored by physiologists and pharmacologists alike, for estimating the effect of procedures and of drugs that influence sweating. From the classical paper of Max Levy[15] in 1892 to the studies of Hasama[16] nearly forty years later, it has been the chief method of estimating sudorific responses.

Burn's investigations,[17] which were limited to a consideration of the peripheral mechanisms in animals and which carried the subject about as far as laboratory methods permit, led to the conclusions: That pilocarpine had a dilator action on the vessels; that after denervation of the leg a sweat response to pilocarpine persists only so long as vaso-dilatation persists; that the loss of the sweating and dilator response is not due to

degeneration of the sympathetic or sensory nerve fibres but rather to degeneration of the motor fibres of the leg muscles; that the amount of sweat secretion produced by a central stimulus depends upon the blood-flow through the foot-pads; that the exaggeration of the sweat responses to pilocarpine after sympathetic degeneration is due mainly to removal of sympathetic control of the blood-vessels.

In contrast to Burn's laboratory observations, in which the possible active participation of the parasympathetic system in the phenomenon of sweating does not seem to have been considered, one may turn to the observations on man which have already been made and which are likely to be made in still greater number in the future now that the involuntary nervous system has come to be the object of attack by surgeons. The most informing and most detailed studies so far reported are those by Otfrid Foerster and by his co-workers, Guttmann and List,[18] the results of which are assembled in the concluding sections of Foerster's elaborate treatise on the effect of gunshot wounds on the peripheral nerves.[19]

Foerster assumes the existence, for the diaphoretic mechanism, of a higher diencephalic and a lower bulbar center whence the fibres descend in the cord to emerge by way of the anterior spinal roots. He has found that stimulation of a posterior root after its division causes vaso-dilatation confined to the spinal dermatome concerned, whereas subsequent stimulation of the corresponding anterior root causes sweating and a pilomotor response without vaso-dilatation over a much wider field, the central strip which previously showed vaso-dilatation from posterior root division remaining dry. Thus sweat fibres unquestionably leave the cord by the anterior root and active efferent vaso-dilator fibres by the posterior root, the two acting quite independently.

Foerster has further shown: That stimulation of purely sensory peripheral nerves causes both sweating and vaso-dilatation in the area of cutaneous distribution; that total division of a mixed nerve leads to significant vaso-dilatation over the area of its cutaneous distribution, and though in some cases pilocarpine may continue to cause sweating in this area, it soon loses this effect with resultant total anhidrosis; and that division of the sympathetic paths completely checks the hyperhidrosis produced by external heat, but does not in any way affect that induced by pilocarpine. In other words, sweating produced by external heat and by pilocarpine act somewhat differently. From these and other observations Foerster had been led to conclude that in the peripheral nerves there are two sets of sweat fibres, one sympathetic and the other set, which reacts to pilocarpine, parasympathetic. Where the latter have their higher centers and how the fibres run in the peripheral nerves he does not pretend to say.*

* By electrically stimulating the surfaces of the serially transected brain and medulla

The investigations by Burn on animals and by Foerster on man which have thus been briefly reviewed have been restricted, as we have seen, to the peripheral mechanisms concerned in vaso-dilatation and sweating; and though Foerster at least predicated the existence of higher centers of control, these had not been made the particular object of a detailed study until the matter was taken up by Hasama, a Japanese pharmacologist. In his three important papers[15] Hasama has shown elaborately and conclusively that mechanical, thermic, chemical and electrical methods will all serve to affect both sweating and the thermo-regulatory apparatus, whether the stimulus is applied to centers in the interbrain or to others which presumably are directly subsidiary and which lie in the floor of the fourth ventricle, more especially the dorsal nucleus of the vagus. As Hans Meyer was led to predicate the existence of separate warming and cooling centers, one sympathetic and the other parasympathetic, so Hasama has concluded from his studies that there are two kinds of centrally induced sweating, one parasympathetic associated with vaso-dilation, and the other sympathetic or "cold" sweating.

But it is fair to say that neither mechanical, thermic, chemical or pharmacological excitation, however much information may be gained thereby, represents the natural way of affecting the diencephalic centers with which we are concerned; and reasons have been advanced whereby it may be at least assumed that the posterior lobe hormone may actually be the normal excitant, albeit the extract must be administered in a far larger dose than normally is present in order that we may unmistakably recognize its effects. And one striking feature of this vaso-dilator and diaphoretic response called forth by pituitrin is the surprising coincidental antipyretic effect, the like of which does not seem to have been observed or to occur in animals.

Conclusions.—The information in this series of papers, on which an hypothesis has been built up regarding the action of the posterior pituitary hormone on an assumed parasympathetic center in the interbrain, may be briefly summarized as follows:

(A) The active principle of the neurohypophysis is in part excreted into the blood-stream and in part into the cerebrospinal fluid. The hormone when experimentally introduced into the blood-stream causes pallor from vaso-constriction and stimulates the musculature of the lower bowel; when introduced into the ventricle, on the contrary, it causes flushing, sweating, salivation, lachrymation, vomiting and a pronounced fall in body temperature. The former bears resemblance to a sympathetic discharge combined with a sacro-autonomic effect; the latter appears

of the cat, Langworthy and Richter (Brain, 1930) **53**, 178, have traced the autonomic paths for sudorific impulses from the frontal cortex through the diencephalon to the spinal cord.

to be essentially a cranial autonomic or parasympathetic effect. Pilocarpine introduced into the ventricle gives a highly similar response.

These responses to intraventricular pituitrin and pilocarpine are counteracted by atropine whether given subcutaneously or intraventricularly; they moreover appear to be abolished when the tuberal portion of the interbrain is highly distended by hydrocephalus or is the seat of tumour; and their action furthermore is checked by tribromethanol, a narcotic that presumably acts chiefly on the interbrain.

(B) A rich arborization of unmyelinated nerve fibres is known to pass from the tuberal nerve centers to ramify in the neurohypophysis. The posterior pituitary hormone or a substance indistinguishable from it has been shown to be increased in the cerebrospinal fluid after electrical stimulation of the tuber. It has also been shown to be increased in amount in the fluid of animals under emotional excitement. The interbrain has been shown to be the seat of the primitive emotions which are released from their cortical inhibitions by experimentally disconnecting the nerve paths from the frontal cortex. Theoretically animals so decorticated should show an increase of posterior pituitary hormone in the cerebrospinal fluid.

(C) As a working concept it may be assumed: (1) That under emotional stimuli the posterior pituitary becomes discharged through its specific and histologically demonstrable diencephalohypophysial mechanism; (2) that the active principle or a portion of it enters the cerebrospinal fluid whence presumably by diffusion through the ependyma it may come to act upon diencephalic nuclei for the parasympathetic apparatus; (3) that conditions may conceivably arise when posterior pituitary hormone is discharged into the fluid in sufficient strength to call forth a parasympathetic (cranial autonomic) response as diffuse in its character as is the response on the part of the sympathetic system brought about by the discharge of adrenalin. The neuro-hypophysis, in short, may conceivably bear a somewhat similar relation to the parasympathetic division that the adrenal medulla does to the sympathetic division of the autonomic nervous system.

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THE INADEQUACY OF THE SUB-GENE HYPOTHESIS OF THE NATURE OF THE SCUTE ALLELOMORPHS OF DROSOPHILA

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In a series of papers, Serebrovsky (1930), Dubinin (1929), Agol (1930) and their colleagues have described an extremely interesting group of bristle-reducing mutant genes lying at the scute locus of the X-chromosome of Drosophila melanogaster. As a result of their careful studies of this material, they have elaborated an interpretation of the situation. According to this hypothesis, the normal allelomorph of the scute genes is not a single unit, but is made up of a series of "sub-genes" arranged in linear order, each sub-gene being concerned with the development of one or of a few bristles on the fly. The scute mutations involve changes in blocks of these sub-genes, but of different blocks. Scute 11, for example, represents mutation of a few sub-genes at the left end of the series; scute 4, of practically all the sub-genes not affected by scute 11; scute 5 of a few sub-genes near the right end. All the known allelomorphs may be described in such terms.

Serebrovsky has arranged the bristles in a linear series, that he takes to correspond to the linear series of sub-genes. From our own data,[1] which include a few additional bristles, we have constructed a linear series, paying particular attention to variations in amount of effect. The resulting seriation of bristles is substantially the same as Serebrovsky's, though we believe it to be slightly more accurate, and to be capable of still further improvement. This seriation is: 1, p. dorsocentral; 2, a. dorsocentral; 3, p. supra-alar; 4, inner vertical; 5, "ventral;" 6, p. postalar; 7, presutural; 8, p. orbital; 9, a. supra-alar; 10, outer vertical; 11, a. postalar; 12, a. notopleural; 13, middle orbital; 14, ocellar; 15, postvertical; 16, a. orbital; 17, coxals; 18, sternopleural; 19, p. scutellar; 20, a. scutellar; 21, humerals. Using this series as a base-line, we have drawn a curve for each scute allelomorph, showing its effectiveness in removing the successive bristles. Most of the allelomorphs give smooth unimodal curves. The irregularities that do exist may be due to modifying genes at other loci, or they may present real difficulties. It should be emphasized that these remarks apply to our own data, based on male flies only. In other words, Serebrovsky's seriation may be derived and further elaborated without using the data from heterozygous females, except insofar as these data are necessary to establish that the genes dealt with belong to one series of allelomorphs.

In a recent communication Agol (1930) has presented briefly what he

believes to be a striking confirmation of this theory. He has studied the behavior of scute in the presence of the deleted chromosomes induced by x-rays. If the hypothesis is correct, occasionally chromosomes should be broken within a gene, and fragments result lacking some of the sub-genes within a given locus. Such fragments should suppress the effects of the sub-genes which they themselves contain; but the characteristic effects of those to the right of the break should appear as usual. These expectations have been fulfilled, offering what may appear to be a complete verification of the guiding hypothesis.

On closer examination, certain difficulties appear. In the first place, Agol's results may be interpreted as due to the occurrence of a new scute allelomorph in the deletion at the time of breakage. Since scute is a rather mutable locus, it is by no means unlikely that out of a number of deletions tested, some should contain new allelomorphs. Even assuming, however, that no mutation to a scute allelomorph occurred, there remains the possibility that the dominance relations at the scute locus are different in the presence of the deletion. It is well known that the dominance relations between a gene and its normal allelomorph are affected by changes in the rest of the genetic system (see Bridges in Morgan, Bridges and Sturtevant, 1925). For example, in the case of the original Pale-translocation of Bridges, the included gene, plexus, presents a greater dominance effect in the flies carrying two doses of plexus and the normal allelomorph in the duplication than is seen in triploids with two doses of plexus and one normal allelomorph.

In the present case, the question is whether or not the dominance of scute in Agol's experiments may be a property of other portions of the X. This may be tested by studying the behavior of scute with duplications [2] which all include scute itself and in addition other varying portions of the X-chromosome. We have done this, and our data indicate that scute may under certain circumstances behave as a dominant, particularly for bristles in the right portion of Serebrovsky's linear map.

This is particularly well shown in experiments (Table 1) with Translocation X-1, an X to III translocation discovered and analyzed by Professor H. J. Muller. In this case the break is to the right of the white locus, so that besides scute, the duplication contains a considerable section of X-chromosome. The translocation contains no scute allelomorph, since heterozygous females are substantially normal, and cross-overs for this region have been obtained, giving normal males (those carrying the translocation die). Males carrying the duplication and a normal X present certain abnormalities, similar to those described by Muller (1930). Since they are particularly sensitive to modifiers, all the stocks used were made homogeneous as far as possible, before the experiment proper. Table 1 gives some of the data. The duplication itself produces abnormalities

of bristles occasionally, particularly on the scutellars, which may be absent because of breakage in emergence from the pupa case. For this reason, the apparent effect of yellow 2 on the scutellars is spurious. These are probably unaffected in these modifiers, although in certain cases a real scute effect has been seen.

TABLE 1

MEAN BRISTLE NUMBERS[1]

	POST VERTICAL	ANTERIOR SCUTELLAR	POSTERIOR SCUTELLAR	COXAL I	COXAL III	OCCIPITAL	NUMBER OF FLIES
Dupl. X-1/y^2	1.99	1.86	1.36	1.92	1.00	1.56	66
Dupl. X-1/yac	2.00	1.96	1.92	1.79	0.92	1.35	48
Dupl. X-1/sc^1	1.87	2.00	1.91	1.18	0.32	1.27	45
Dupl. X-1 / sc^1 pn g car	1.53	2.00	1.97	0.79	0.12	1.12	34
Del. 101/ysc^1	2.00	2.00	2.00	1.96	1.97	1.62	50

[1] The means for the coxal III bristles are based on somewhat smaller numbers of flies than are the other values given. The occipitals, absent in the wild-type, are present in most flies that carry duplications for the scute region.

The coxal I bristles give critical evidence. It is obvious that they are strongly affected by scute,[1] and much less so by the others. Even the slight effect in the others is probably due to the admixture of non-disjunctional males which were heterozygous for scute. It is apparent that the removal from a female of a section of the X-chromosome to the right of white produces a male in which scute[1] behaves as a dominant, with respect to certain bristles.

The dominance is for bristles at the right on Serebrovsky's map. With achaete, far to the left on the map, this bristle is probably completely unaffected, as is to be expected if the dominance effect is a function of the particular scute allelomorph. Data on other scute allelomorphs, with modifiers as yet uncontrolled, support this obviously plausible view. Dominance is also a function of the modifiers in the system, as is shown by the data from Duplication X-1/sc^1 pn g car, where the indication of a post-vertical effect is strengthened, and all the other effects are more extreme.

Several other duplications for this region give similar results. If, however, the break occurs still further to the left, leaving a fragment which includes only yellow, scute and silver, different relations appear (Del. 101/y sc^1 in table 1). In this case scute is practically completely recessive. We must assume then, that there are at least three portions of the X concerned with the scute effect—a portion at the middle, tending to make scute recessive; a more distal portion (svr–w) which enhances its effect; and the normal allelomorph of scute itself. This is in complete harmony with the view that the dominance of any one gene is a function of the system as a whole. If this is granted it becomes difficult to accept the proof of the sub-gene hypothesis offered by Agol.

This view of dominance raises other difficulties for the Serebrovsky hypothesis. It implies that the developmental system is a system in which limiting factors are important, and in which, therefore, changes in the rest of the system make changes in threshold values. That thresholds are important in the all or none systems concerned with the absence of bristles is obvious, as will be shown further.

Lewit (1930) raises the question whether it may not become necessary to postulate that each scute allelomorph affects many bristles outside the region in which its action is normally detected. His own data suggest that such effects may be produced on bristles that lie (on Serebrovsky's map) adjacent to the known field of action of the given scute allelomorph. We have evidence that indicates such effects on bristles lying very remote from the known field of action. Achaete lies at the extreme left of Serebrovsky's map, scute 1 covers most of the right half. The scute 1-achaete heterozygote is completely normal; but both act as allelomorphs to scute 3, which on Serebrovsky's interpretation is to be taken as resulting from mutation of practically the entire series of sub-genes. We have studied scute 1 and achaete in flies that were also Hairless (the gene concerned is a III-chromosome dominant that removes bristles in a pattern different from that of the scutes—Plunkett (1926).[3] The table shows the results obtained for a few bristles.

TABLE 2

AVERAGE NUMBER OF BRISTLES

	INNER VERTICAL	ANTERIOR DORSOCENTRAL	POSTERIOR SUPRA-ALAR	POSTERIOR ORBITAL	OCELLARS	HUMERALS	NUMBER OF FLIES
$H\ \frac{+}{+}$	1.65	1.61	0.62	0.82	1.94	2.60	80
$H\ \frac{+}{sc^1}$	1.98	1.78	0.86	1.16	1.96	2.94	50
$H\ \frac{+}{ac}$	1.46	1.49	0.38	1.04	1.89	2.56	80
$H\ \frac{sc^1}{ac}$	0.80	0.80	0.02	0.52	1.57	2.02	60

In each series 22 different bristles were recorded for each side of each fly: in only one case did the $H\ \frac{sc^1}{ac}$ class have an average value higher than that of any one of the other three classes—and that difference (anterior supra-alar, 1.92 for $\frac{sc^1}{ac}$, 1.89 for $\frac{+}{ac}$) was certainly not significant. The table shows only a few of the more extreme cases; but it must be noted that these bristles are scattered throughout Serebrovsky's map: the inner vertical and the humerals are usually placed at opposite ends, and the others listed are scattered through the whole range. It should also be noted that, with this same set of modifiers (exclusive of Hairless) our data show that the inner vertical and posterior supra-alar are not affected either by achaete or by scute 1 alone. Hairless serves here only as a sensitizer,

making the effects of scute 1 and of achaete more obvious: the data given leave no alternative to the conclusion that both scute 1 and achaete are acting on bristles scattered throughout the entire length of Serebrovsky's map, though many of these effects, under ordinary conditions, are of sub-threshold degree.

This conclusion is in harmony with most recent ideas concerning the way in which genes control development. It seems to us to destroy the value, as a working hypothesis, of the extreme preformationist sub-gene hypothesis. If each scute sub-gene is affecting many or all of the bristles of the fly, the whole logical basis of the hypothesis is undermined.

The remarkable series of facts described by the Russian investigators remains. If the bristles are plotted on a picture of the fly in the order indicated above, the impression is strong that there is a real pattern present, with a single center in the median line near the level of the posterior dorso-central. Following the suggestion of Plunkett (1926), the pattern may be thought of as resulting from the diffusion of some substance from this center, not with equal speed in all directions, but more rapidly anteriorly, with occasional lateral outpushings. In any case, on this or some similar basis one may interpret the scute allelomorphs as acting at specific times during this process. This conception has already proved useful in that it led to the supposition that there might be an effect of some of the more "peripheral" scutes on the bristles of the "filter-apparatus" (Frey, 1918) in the pharynx—a supposition that we have verified for scute 3, scute 4 and scute 7.[4]

Finally, the behavior of the scute allelomorphs in heterozygous females, used by Serebrovsky as the basis of his map, raises no difficulties for the hypothesis here suggested. For these reasons and from general considerations we prefer to look for the solution of the linear series discovered by the Russian workers in some such developmental interpretation as this rather than in hypotheses as to the structure of genes.

[1] We are greatly indebted to Prof. A. S. Serebrovsky for his generosity in sending to this laboratory stocks of scute 2, scute 3, scute 4, scute 5, scute 6, scute 7 and scute 11, as well as of several other interesting new types. The other types examined were scute 1, scute B3 (the scute 3 of Morgan, Bridges and Sturtevant, 1925), achaete, and scute D (recently obtained by Prof. T. Dobzhansky in x-ray experiments, and very kindly given to us by him).

[2] It is a pleasure to express our indebtedness to Professor H. J. Muller, to Professor T. Dobzhansky and to L. V. Morgan, for their kindness in supplying us with stocks of the various duplications.

[3] The races used in these experiments were all put through a process of inbreeding and crossing that should have made them uniform for all genes except those lying near the scute and hairless loci. We have also used most of the precautions suggested by Plunkett (1926) to insure environmental uniformity.

[4] The wing and abdomen effect of scute 2 and scute 9 (Dubinin 1929, Lewit 1930) is probably also to be referred to the pharyngeal region, as the abdominal ab-

normality is evidently an inflation of the crop, which Eidmann (1924) has shown to be concerned in the hydrostatic mechanism of wing expansion; and the opening of the crop into the oesophagus, its only connection to the surface, is in the head.

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PROOF THAT BAR CHANGES TO NOT-BAR BY UNEQUAL CROSSING-OVER

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The hypothesis of unequal crossing-over at the bar locus in the X-chromosome of *Drosophila melanogaster*, advanced by Sturtevant to account for so-called reversion of bar, has been fully supported by his experimental evidence.[1] By use of the characters forked and fused combined with bar and a new allelomorph, infrabar, he showed that "sixteen different kinds of changes at the bar locus" occur "exclusively, or nearly so, in eggs that undergo crossing-over at or near the bar locus."

Sturtevant noted, however, in the data on the changes at the bar locus a deficit in one class of individuals, namely, double-bar. "This hypothesis makes reverted round and double-bar complementary cross-overs, and they

should accordingly be produced with equal frequency. Table 1 agrees with Zeleny's more extensive data in showing that round is far more frequent than double-bar, but such a result was to be expected for two reasons. Double-bar is not as viable as round, so that fewer of the double-bar mutant individuals would be expected to survive; and double-bar is not always clearly distinguishable from bar, so that some mutant individuals are probably overlooked, while it is not likely that any reversion is overlooked through difficulty of classification" (loc. cit., p. 122). (A corresponding deficit was observed in the case of infrabar (loc. cit., p. 126).) Later experiments[2] confirmed all the previous results and showed the viability of double-bar to be 75% that of round, and improved technique lowered the ratio of observed numbers of round and double-bar from 3.5:1 to 1.9:1.

The explanation of the deficit of double-bar individuals is convincing and, as Dr. Sturtevant pointed out, the only evidence for the hypothesis that might be added would be a demonstration of the production of the two complementary kinds of chromosomes at one event of crossing-over. Such a demonstration has now been found in the analysis of a non-disjunctional daughter of a homozygous bar female. She was discovered because of her exceptionally narrow eyes in a mass culture of yellow males mated to females homozygous for bar whose X-chromosomes were attached; the females were therefore non-disjunctional and were bar over bar $\left(\frac{B}{B}\right)$. The narrow eyes of the exceptional fly were due presumably to two genes for bar being in the same chromosome. When this occurs, Sturtevant has found that the eyes are narrower than in homozygous bar. Not only is this true when in the opposite chromosome bar is present $\left(\frac{BB}{B}\right)$, but also when no bar is present there $\left(\frac{BB}{+}\right)$. The facet number for $\frac{BB}{+}$ is 45.4 and for $\frac{B}{B}$ 68.1. If the narrow-eyed fly were $\frac{BB}{B}$, only one of her chromosomes was a cross-over; but if she were $\frac{BB}{+}$, then both chromosomes were cross-overs and were of the complementary types due to unequal crossing-over.

To test her constitution, the narrow-eyed fly was mated to yellow males. About 5.1% of homozygosis for forked occurs in attached X's when one of them carries forked; hence, if the narrow-eyed female were of the constitution $\frac{BB}{+}$, about 5% of her daughters (bar being only 0.2 units to the right of forked) should be round; but if she were $\frac{BB}{B}$ none of her

daughters would be round. (The possibility that she was $\frac{B}{B}$ and that the narrow eyes were due to a modifier was also put to the test by the same experiment, because she would then produce no round daughters.) She gave, in fact, in F_1, about 56 narrow bar-eyed females like herself, and 3 round-eyed females. Also in an F_2 mass culture from F_1 narrow bar daughters there were 93 narrow bar-eyed to 6 round-eyed females. The number of round-eyed flies is clearly too large to be due to reversion of bar to round and is nearly the 5% to be expected from crossing-over.

The fact that the constitution of the narrow-eyed fly was double-bar over round $\frac{BB}{+}$, added to Sturtevant's evidence for crossing-over when reversion occurs, supplies the final proof of his hypothesis. It shows that a reverted chromosome (+) and a chromosome showing unequal crossing-over by the presence of two genes for bar (*BB*) originated together in the same egg from two bar chromosomes. Reversion of bar to not-bar was the result of unequal crossing-over at the bar locus.

[1] Sturtevant, A. H., "The Effects of Unequal Crossing Over at the Bar Locus in Drosophila," *Genetics*, **10**, 117–147 (1925).

[2] Sturtevant, A. H. "A Further Study of the So-called Mutation at the Bar Locus of Drosophila," *Genetics*, **13**, 401–409 (1929).

DIFFERENCES BETWEEN CHROMOSOME GROUPS OF SOMA AND GERM-LINE IN SCIARA[1]

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In our earlier studies on chromosomes in Sciara[2] the customary assumption was made that the fundamental chromosome group of an individual is constant throughout the different tissues of the body, somatic and germinal. Consequently, the tissues most easily studied were used in identifying the chromosome groups of the male and female, respectively, in the species used. Because of their favorability in this respect the ovarian follicle cells, on the one hand, and the spermatogonia and spermatocytes on the other were used for the chromosome studies.

These studies revealed a consistent difference between the chromosome groups of the two sexes; the female group possessed four pairs of chromosomes and the male group the same four pairs plus two larger chromosomes,

referred to as "sex-limited" or "male-limited." (In the present account these will be designated the "limited" chromosomes.) Since cytological study of spermatogenesis indicated that both of the latter chromosomes are transmitted by all sperms, it was concluded that they are confined to males, presumably being eliminated by female-producing zygotes during cleavage.

Recent studies, however, have thrown an entirely new light on the situation by showing that in both sexes the chromosome group of the soma apparently differs from that of the germ-line, and that conditions in the female differ from those in the male. The results as regards the male have been considered previously in a more detailed account.[3]

The present note is concerned primarily with conditions in the female. The account is based on one species, *Sciara coprophila* Lintner, but presumably applies also to others in which only spermatogonia and ovarian follicle cells have been examined. (See Metz, '26, loc. cit.)

Chromosomes of the Male.—The spermatogonial chromosome group typically includes ten chromosomes, of which two are much larger than the others. These two are the above-mentioned "limited" chromosomes. Frequently one of them is lacking or is represented by a fragment, and occasionally three are present. Spermatocyte figures corroborate this analysis of the group, as indicated in the papers cited above. Figure 1 represents a spermatogonial group containing only one of these large chromosomes. In contrast to the group found in the germ-line, that observed in male somatic cells contains only seven chromosomes, as indicated in figure 2. This group lacks both of the large "limited" chromosomes and also one of the smaller rod-like members.

Chromosomes of the Female.—In the female a comparable, but different, condition apparently exists. The somatic group consists of eight chromosomes (figure 3) instead of seven as in the male. The group in the female germ-line is very difficult to study (see below) and present results are conflicting; but in some cases, at least, this group appears to be the same as that in the male germ-line. One such group is shown in figure 4. Apparently this is also from material in which only one of the "limited' chromosomes is present, since it contains nine instead of ten members.

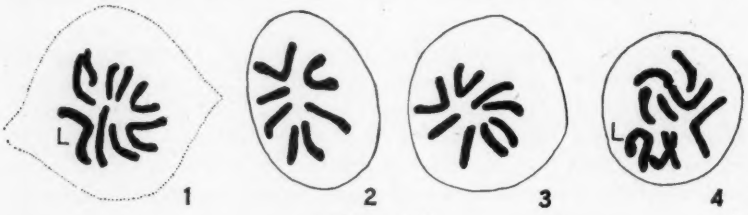
Two difficulties are encountered in trying to identify the typical germline group in the female. One is due to the fact that oogonial figures can only be secured at a very early embryonic stage when the ovary is indistinguishable from the testis (by any criteria thus far discovered). This fact makes doubtful the identification of any particular gonad as an ovary at such a stage. The difficulty is largely obviated, however, by the use of embryos from "unisexual" female progenies. (See Metz '26 and '29, loc. cit.)

The second difficulty is not so easily avoided. It concerns the nature of

the large, "limited" chromosomes, and the possibility that in the oogonia these chromosomes occur only as large fragments. This feature is discussed in the last two paragraphs. In any event, however, the "limited" chromosomes or fragments observed in the oogonia are not seen in any of the scores of somatic figures thus far examined.

In addition to oogonial figures of the above type, others have been observed with smaller chromosome numbers, ranging from four to seven. It is probable that these deficient groups are present only in restricted clusters of oogonia and are not characteristic of the entire ovary in any case. Since present evidence is insufficient to reveal their true significance, they are left out of account here.

Chromosome Elimination.—Although the actual process of chromosome elimination from somatic nuclei has not yet been studied, the above evi-



FIGURES 1–4

Chromosomes in *Sciara coprophila* Lintner. Figure 1, spermatogonial group. Figure 2, somatic group of male. Figure 3, somatic group of female. Figure 4, oogonial group. (L), the "limited" chromosome. In comparing these groups it should be borne in mind that, whereas homologous chromosomes maintain a paired association in somatic cells, they apparently do not do this in oogonia or spermatogonia. It should also be noted that in figures 1 and 4 the chromosomes do not all lie in a horizontal plane; hence there is some distortion due to foreshortening.

dence requires the assumption that such a process does occur. Presumably it takes place during early cleavage.[4] In both sexes it involves the elimination of the "limited" chromosomes, which thus apparently become restricted to the germ-line. So far as present evidence goes this limitation applies as well to fragments as to entire chromosomes. In the female the process affects only the chromosomes just mentioned, but in the male one of the small rod-like "ordinary" chromosomes is also eliminated. This is presumably a sex chromosome. As noted elsewhere[4] the elimination of this chromosome may be concerned with sex determination, and may lead to an interpretation of sex determination quite different from those suggested in our earlier accounts.

The "Limited" Chromosomes.—In the female, as in the male, the study of somatic chromosomes has not extended to all the tissues. In some tissues the cells are very small and the figures difficult to study. Many

good figures have been found in ovarian follicle cells and a few excellent ones in other somatic tissues. All these agree as to make-up and serve, in our opinion, to justify the tentative assumption that they represent the typical somatic group of this sex.

This fact, taken in connection with the similar evidence respecting the male somatic group, points strongly to the conclusion that in both sexes the "limited" chromosomes are restricted to the germ-line. Presumably their function is likewise restricted to influences on the development of the gonads or germ cells. They may, perhaps, be referred to as "gonosomes."

The presence of these chromosomes in the female raises additional questions concerning both their intrinsic nature or composition and their mode of transmission. Studies on spermatocytes, as noted in earlier papers, have shown that they vary in number and have a tendency to fractionate. Fragments of varying size and number have been observed frequently (see, e.g., Metz, Moses and Hoppe, loc. cit., Figs. 20 and 21). These fragments, even when numerous, however, have no observable effect on the sex or genetic behavior of the fly. Such observations indicate that in spite of their large size the "limited" chromosomes carry relatively few genes (Metz '29, loc. cit.) and that the genes are probably restricted to the terminal regions of the chromosomes. The latter inference is drawn from the fact that the fragments appear to include the central region, including the point of spindle fibre attachment, rather than the terminal regions of the chromosome. Cytological evidence has also indicated (Metz, Moses and Hoppe, loc. cit.) that the full number of these chromosomes present in the male is transmitted by all sperms. It seems possible, therefore, that the "limited" chromosomes observed in oogonia are not entire, but are merely unusually large fragments. Such an interpretation receives some support from the fact that, according to unpublished evidence of Mr. Adrian Ter Louw, small fragments, when present, are transmitted as readily by females as males.

In any event, the presence of the "limited" chromosomes in oogonia indicates that a regulatory process of some kind must occur to keep the number from multiplying indefinitely, whether these are whole chromosomes or fragments. This feature is under investigation by Mr. Adrian Ter Louw.

[1] This investigation has been aided by a grant from the NATIONAL RESEARCH COUNCIL, Committee for Research in Problems of Sex.

[2] E.g., Metz, '25, *Science*, n.s., **61**, 212; Metz, '26, *Amer. Nat.*, **60**, 42; Metz, '29, *Amer. Nat.*, **63**, 487; Metz, Moses and Hoppe, '26, *Zeits. ind. Abs. Vererb.*, **42**, 237.

[3] *Biologische Zentralblatt*, 1931, No. 3. They were first presented at the International Congress for Sex Research in London, Aug. 5, 1930.

[4] This feature is discussed in the paper referred to in footnote 3.

THE HEREDITARY BASIS FOR MELANOSIS IN HYBRIDS OF MEXICAN KILLIFISHES

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In the *American Journal of Cancer* for April, 1931, there has just appeared a paper by the writer on the "Morphology of the heritable color patterns in the Mexican killifish, Platypoecilus." It is the first of a series of three papers, two of which are to appear in the July number of that journal. The present communication summarizes the chief features of the two unpublished papers: one is concerned with the hereditary basis for the occurrence of melanosis in hybrids between certain genetic varieties of Platypoecilus and Xiphophorus, and the other discusses the morphology of the melanotic hybrids with respect to the melanotic state in general and melanotic tumors in particular.

The Melanotic State.—Melanosis in hybrid fishes (*Platypoecilus maculatus* by *Xiphophorus hellerii*) is a condition characterized by an excessive growth of large black pigment cells. Normal tissues of the dermis are invaded and replaced by black chromatophores. The degree of melanosis shown by the individual hybrid fish varies. For purposes of description the advance of melanosis will be mentioned as occurring in a system of three states of intensity. As intermediate stages between these three states of melanosis have been observed within fishes of a given brood, it is believed that all of the melanotic hybrids express different states of the same pigmentary disturbance.

The initial state of melanosis is characterized by the replacement of the normal tissues in the dermis by macromelanophores. Large areas are invaded but the growth process of melanophores does not involve the loss of body parts. The initial stage may be recognized on the day of birth of the hybrids and there is every reason to believe it may be detected even during the period of larval development within the oviduct of the gravid female.

In the second progressive state of melanosis there is a further invasion of the dermal regions, accompanied by a deterioration of the structural elements themselves. The scales and fin rays are divested of their soft parts and there is a noticeable loss of rays especially in the dorsal and caudal fins. Correlated with the loss of dermal areas is the invasion of subcutaneous tissues by macromelanophores and the replacement of connective tissues associated with muscle and bone.

The third state of melanosis may be characterized by the development of large melanotic overgrowths in various parts of the body. In some

cases the tumor is the size of the head while in others the entire posterior part of the body is greatly enlarged. Histological preparations of these melanotic overgrowths reveal neoplastic features. (On this point our diagnosis is confirmed by the following well-known workers in cancer, who have examined the material: Professor James Ewing, Dr. Francis Carter Wood and Dr. James B. Murphy.)

Relation of Color Pattern of Parent to Type of Hybrid Offspring.—An analysis of the results of fish fanciers and geneticists reveals the fact that whenever the pulchra, rubra and under certain conditions nigra (black) varieties of *Platypoecilus* are used in generic crosses with the swordtail, *Xiphophorus*, melanosis develops in one half or all of the hybrid fishes.

On the other hand when varieties of the platyfish, other than the pulchra, rubra and nigra are used, no comparable melanotic conditions appear among the generic hybrids. The following varieties have been tried and have given negative results with respect to melanosis: gold, stippled, one-spot, twin-spot and crescent platyfish.

An explanation of the above results may be gained by a study of the morphology and genetics of the pigmentary equipment of the various color patterns in Platypoecilus. In an extended study of the morphology of the heritable color patterns in Platypoecilus and Xiphophorus, the writer (1929, 1931) analyzed all the parent types which have been used in these intergeneric crosses. The following table summarizes the pigmentary elements involved and the varieties in which they are found:

TABLE 1

ANALYSIS OF THE HERITABLE COLOR PATTERN ELEMENTS IN THE VARIETIES OF PLATYPOECILUS

GENETIC RACE OF PLATYPOECILUS	MELANOPHORES		ERYTHROPHORES	
	MACRO SPOTS[2]	MICRO STIPPLES[3]	*Rf*[4] RED FINS	*R* RED BODY
1. Gold platy*	..	..	*Rf*	..
2. Red platy*	..	..	*Rf*	*R*
3. Stipple platy*	..	*St*	*Rf*	..
4. Stipple, crescent	..	*St*	*Rf*	..
5. Stipple, one-spot*	..	*St*	*Rf*	..
6. Stipple, twin-spot*	..	*St*	*Rf*	..
7. Red, spotted*	*Sp*[1]	..	*Rf*	*R*
8. Nigra	*Sp*	*St*	*Rf* or *rf*	..
9. Pulchra	*Sp*	*St*	*Rf* or *rf*	..
10. Rubra*	*Sp*	*St*	*Rf*	*R*

[1] The presence of the symbol *Sp* indicates that spots (macromelanophores) appear in the variety.

[2] Spots are made up of a group of macromelanophores.

[3] Stipples refer to micromelanophores.

[4] *Rf* is the genetic symbol for red fins. (Its inheritance is poorly known.)

* Indicates that these varieties have been used in the experiments at Cornell University laboratory.

The Hereditary Basis for Color Patterns.—In 1927 the writer showed genetically that there were two kinds of melanophores in the rubra platy. The pigmentary elements which are responsible for large black spots are macro-melanophores and their hereditary behavior is conditioned by a sex-linked dominant factor (*Sp*). The small black pigment cells responsible for the underlying stippling and olivaceous color, the micromelanophores, are conditioned by an autosomal dominant factor (*St*).

The nigra pattern formed by macromelanophores, arranged in a dense row along the sides, is conditioned by a dominant sex-linked gene (*N*) according to Bellamy (1928) and this is confirmed by unpublished data obtained in this laboratory.

The red body color due to erythrophores is conditioned by the sex-linked dominant factor *R* (Fraser and Gordon, 1929), while the red fin complex seems to be due to an autosomal dominant factor *Rf*, although Kosswig thinks it is sex-linked.

The other patterns involved in intergeneric crosses: stippled, one-spot, twin-spot and crescent are formed by micromelanophores. Specific differences in melanophore distribution determine the pattern characteristics in each variety. Each pattern is conditioned by a distinct dominant autosomal gene (Gordon 1927, 1931).

Relation of Color Pattern of Parents to Type of Hybrid Offspring.—Each genetic race of Platypoecilus has been crossed with Xiphophorus in order to determine which color varieties are associated with the occurrence of melanosis in the hybrid progeny. The varieties tested are listed in table 1, to which have been added several strains employed by other workers. In the first series of crosses made at this laboratory the following results were obtained:

TABLE 2

XIPHOPHORUS FEMALE	×	PLATYPOECILUS MALE	=	TYPES OF HYBRIDS: MELANOTIC* 1	2	3	NON-MELANOTIC	TOTAL
Stipple (*St'St'*)		Gold (*RfRf*)		0	0	0	8 red-finned, stipple	8
Stipple (*St'St'*)		Red (*RR*)		0	0	0	13 red, stippled	13
Stipple (*St'St'*)		Rubra (*RrSpspStst*)		5	0	0	6 stippled	11
Male		Female						
Stipple (*St'St'*)		Rubra (*RRSpSpStSt*)		30	12	3	0	45
								77

* The melanotic fishes are separated into three classes according to the state of melanosis.

As table 2 indicates, when the gold or red platyfish are used as parents only non-melanotic hybrids result; but when the rubra platy is used melanosis appears in all of those hybrids which have inherited the factor

for macromelanophores (*Sp*). Three states of melanosis are indicated. Haussler (1928) and Kosswig (1929) have provided further data on some of these crosses which are in agreement with the facts presented here.

Since the parent platyfish which have given melanotic hybrids (pulchra, rubra, nigra) have all possessed both types of melanophores (table 1) it seemed desirable to test each melanophore factor (*Sp* and *St*) to determine which one is necessary for melanosis in the hybrids. A lead in this direction has been obtained from the work of Gerschler (1914) who crosses the stipple platy (*St*) with Xiphophorus and reported no melanotic hybrids. It would seem, then, that the macromelanophores (*Sp*) were alone responsible for melanosis in hybrids. The latter conclusion has been put to an experimental test by using the following special strain of Platypoecilus, recessive for the stipple factor but heterozygous for spots:

XIPHOPHORUS MALE	×	PLATYPOECILUS FEMALE	=	TYPES OF HYBRIDS
Stipple (*St'St'*)		Red, spotted (*RrSpsp*)		6 melanotic (2d state), 6 stippled

From the above cross it may be seen that it is the factor for macromelanophores which is necessary for the production of melanotic hybrids. It is brought about by the interaction of the *Sp* factor for macromelanophores of Platypoecilus with the modifying factors contributed to the hybrids by Xiphophorus. Further evidence for this has been obtained from the following series of crosses:

In table 2 it has been pointed out that a rubra platy female when crossed with a stippled (normal type) Xiphophorus male produced forty-five melanotic hybrids. The same rubra platy female parent was then crossed to a stippled platy male and as a result of this second mating produced two other broods containing thirty-two spotted fishes. But in none of these latter fishes were there any indications of melanosis. These data show that the genus Xiphophorus contributes certain factors which interact with the macromelanophore factor of Platypoecilus with the result that pigmentary abnormalities develop in the hybrids between them.

The modifying factor of Xiphophorus are represented in non-melanotic hybrids as well as in the melanotic ones. This has been determined by crossing a non-melanotic hybrid back to a rubra platy with the result that melanotic fishes were obtained. Previous workers (Preuss, Haussler, Kosswig) have shown that melanotic hybrids, when crossed back to either parent species, produce a number of melanotic offspring. An attempt has been made to determine the genetic nature of the Xiphophorus modifying factors but no positive results have been obtained as yet.

Summary.—1. The spotted varieties of Platypoecilus (pulchra, rubra, nigra) carry the hereditary factors for *macromelanophores* and when mated to Xiphophorus give rise to melanotic hybrids.

2. Varieties of the platyfish characterized by the possession of *micro-*

melanophores (stipple, one-spot, twin-spot, crescent) or erythrophores (red, gold) when mated to Xiphophorus give rise to normal hybrids.

3. The spotted varieties of Platypoecilus provide the pigment cells (macromelanophores) while Xiphophorus contributes the modifying factors which alter the normal development of the macromelanophores in generic hybrids.

4. Three states of melanosis are recognized in the melanotic hybrids. The third state is characterized by distinct melanotic overgrowths which reveal neoplastic features histologically.

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THE RESPONSES OF THE DEEP-SEATED MELANOPHORES IN THE FROG TO ADRENALIN AND PITUITRIN

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The color changes of cold-blooded vertebrates are caused chiefly by the activity of the melanophores in the skin. Consequently, the responses of these cells have aroused much interest. Frogs placed on a white background or in complete darkness become light-colored due to a contraction of their melanophores. The same result is achieved when adrenalin is injected. If the animals are kept on a black background or are injected with pituitrin, they turn dark through an expansion of the pigment cells of the skin. So far as I know, such observations have not been extended to the melanophores in the deeper parts of the animal. In fact, these cells have received very little attention. Such deep-seated pigment cells are found in the connective tissue of the following regions: the membranous covering of the leg muscles, of the muscles of the back, of the inside of the body wall, the mesenteries, the pericardium, the pleura, the lining of the sub-dermal lymph sacs especially next the skin. The

object of the experiments reported in this paper was to learn whether the reactions of these deep-seated cells are in any way comparable to those of the skin melanophores. The experiments were carried out on the common leopard frog, Rana pipiens Schreber. This species is always dark-skinned under ordinary laboratory conditions. Under the same circumstances the deep-seated melanophores are also expanded, except for occasional cells in the membranous covering of the back-muscles and in the outer layer of the pericardium.

The amount of expansion in the skin melanophores is, however, not always an index to the condition of the deep-seated pigment cells. Although the skin cells contract in about twenty minutes to an injection into the dorsal lymph spaces of 0.5 cc. solution of adrenalin chloride 1:1000 (Parke, Davis and Company), the latter remain expanded for at least an hour after the injection. The first really convincing evidence for movement in these cells occurs about two hours after treatment with adrenalin, when a greater proportion of the pigment cells appear as minute dots or as specks with short, stubby branches. If the frogs are not inspected till three hours after injection, all the melanophores except those on the inner lining of the pericardial cavity will be found contracted. This state of affairs occurred in sixteen cases, while all control animals showed well-expanded cells.

The reaction of the deep-seated melanophores to pituitrin is not so definite as to adrenalin. To be sure, the pigment cells show a finer branching after a 0.5 cc. injection of pituitrin (Parke, Davis and Company, obstetrical) than do those in untreated animals. Yet, the contrast in the amount of expansion is so slight that several other tests are necessary to make the effect of this drug really apparent. The contraction caused by adrenalin persists for more than twenty-four hours, but, toward the end of this period, an expansion will usually occur three hours after an injection of pituitrin. Since an interaction of the two hormones is involved, the true action of the pituitrin may not be singled out. To overcome this difficulty, it is possible to obtain a contraction of the deep-seated melanophores (as well as those in the skin) by putting the frogs either on a white background or in complete darkness. After they are thus lightened, an injection of pituitrin will darken them in the same way as it does after adrenalin. Eighteen frogs thus treated showed an extreme expansion of the pigment cells both superficial and deep, whereas fifteen controls in eighteen showed no expansion.

The results of these experiments indicate that the deep-seated melanophores in frogs behave in much the same manner as those in the skin. Throughout the body, the melanophores contract to an injection of adrenalin as they do when the frog is in complete darkness or on a light background. As expansion of all such cells whether superficial or deep-

seated is obtained with pituitrin or by keeping the animal in dark surroundings. The deep-seated pigment cells respond to stimuli much more slowly than those in the skin. Considering the similarity of the cells, it does not seem strange that the reactions are approximate. Yet, since the skin melanophores are supposed to be concerned with such functions as protective and aggressive coloration, it is hard to conceive what the significance of this activity in the deep-seated pigment cells may be.

CONTROL OF PIGMENT MIGRATION IN THE CHROMATOPHORES OF CRUSTACEANS

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Control of pigment migration in the chromatophores of crustaceans by some specific substance carried in the blood was indicated by the work of Koller[1] in 1925, who injected blood from a black-adapted into a white-adapted shrimp, *Crangon*, and obtained extreme expansion of the chromatophores even though the animal with intact eyes remained on a white background. Expansion of yellow pigment cells was brought about in a white-adapted animal by injecting blood from a yellow-adapted individual, but contraction of chromatophores was not produced by the injection of blood from a white-adapted specimen.

A similar control of chromatophores in another shrimp, *Palaemonetes*, was found by Perkins[2] in 1928 who demonstrated that sea-water extracts of the eye stalks of these animals produced a contraction of the red and the yellow chromatophores when injected into the dorsal sinus of black-adapted or of blinded shrimp. Extracts of other tissues were found to be ineffective in bringing about color changes. The eye stalks were thus identified as the seat of formation of a substance which is carried in the the blood stream to the chromatophores and induces contraction. The means by which expansion is initiated in *Palaemonetes* has not yet been demonstrated.

In 1928 Koller[3] announced confirmation of the eye-extract experiments of Perkins, again using *Crangon*, and in addition demonstrated the expansion of chromatophores by the injection of a sea-water extract of the region under the base of the rostrum. Koller, therefore, postulated two wholly different substances to be present in *Crangon*, one causing contraction and the other expansion of chromatophores. Because of the similarity of these substances to hormones he gave the names "contractin" and

"expantin" to them, respectively. Our attempts to produce expansion of chromatophores in *Palaemonetes* by injecting rostral extract have failed and we are unable to confirm Koller's work in this respect.

Interesting additional evidence of the blood control of pigment is given by Welsh[4] in his paper on the movements of retinal pigments in two Cuban shrimps of the genus *Macrobrachium*. This author found that the ligation of blood vessels leading to the eyes inhibited the distal migration (expansion) of pigment in the eye concerned, while the other eye of the same animal, used as a control, showed normal pigment movement. Using *M. acanthurus*, Smith[5] injected eye extracts and noted subsequent contraction of chromatophores, thus substantiating previous work on *Palaemonetes*.

Kropp[6] has likewise shown that extracts of the eyes of black-adapted tadpoles of *Rana clamitans* produce almost immediate expansion of melanophores when injected into white-adapted individuals. Adult frogs do not show this color change following injection of eye extract, nor does the injection of eye extracts of white-adapted tadpoles bring about the contraction of melanophores. This situation in frog tadpoles was found to hold true also for the fish, *Fundulus*. The expansion effect of eye extracts in these two vertebrates is thus seen to be the reverse of the condition in crustaceans where eye extracts always bring about contraction of chromatophore pigments.

During the course of an investigation into the movements of pigment within the chromatophores of *Palaemonetes*, the results of which will be published later, it became necessary to look for some means of rapidly inducing contraction and expansion of chromatophore pigments in order that their relation to the chromatophore wall might become obvious. At first entire animals were observed in a cell containing running sea water on the stage of the microscope so arranged that superficial chromatophores could be brought to focus under a 4-mm. objective. Pigment expansion was induced by removing the eyes of white-adapted animals, a phenomenon first discovered by Pouchet[7] and repeatedly confirmed by many others, while pigment contraction was brought about by injecting sea-water extracts of Palaemonetes eye stalks. This was a satisfactory means of controlling pigment migration, but the use of an entire animal did not permit proper illumination required for higher powers of magnification.

Subsequently a means was devised by which isolated pieces of tissue containing chromatophores could be closely examined. A black-adapted shrimp was placed under a binocular dissecting microscope and small pieces of transparent shell with their adherent chromatophores were cut from the cephalothorax and abdomen. These pieces were then examined under higher magnification in order to select one with undamaged chroma-

tophores, free from muscle and excessive connective tissue. It was placed on a thin glass cover and a drop of eye extract added. The whole was then inverted and placed over a depression slide previously ringed with vaseline. In preparations of this kind kept for several days bacterial invasion invariably followed, and as it was desirable to make extended observations of pigment movement steps were taken to make a sterile mount. Glassware and instruments were boiled, and the shrimp and pieces removed from it washed in boiled sea water.

Eye extracts were made in the following manner: several fresh or dried eyes were pulverized, a few cubic centimeters of sea water added, and the mass thoroughly mixed. Eyes which had been dried for several months were found to be quite as effective as fresh eyes. After centrifugation the slightly turbid extract was sterilized, thereby throwing down a whitish precipitate, and leaving a perfectly clear liquid. If stoppered with cotton a tube of sterilized eye extract could be kept for several days.

In the intact animal, or in isolated pieces, addition of unheated eye extract induces gradual and almost imperceptible contraction after a refractory period of several minutes, and the fullest degree of contraction is reached only after an hour or more. But when boiled and filtered eye extract is used there follows a remarkably rapid contraction of both red and yellow chromatophores, the first noticeable movements beginning within a few seconds. An entire branch of the chromatophore begins to move proximally as if it were suddenly released from tension, lateral branches are rapidly withdrawn into the main branch and the whole moves as one mass. After proximal migration has proceeded for about two-thirds of the distance toward the center the pigment mass becomes thicker and denser until only a rounded projection from the central sphere can be seen. This projection now flattens out until a completely contracted chromatophore is formed. A very long branch has been seen to reach the intermediate state in thirty seconds, but complete contraction often requires as much as fifteen minutes. Sometimes a rapidly contracting branch shows a slight serpentine movement.

Chromatophores contracted in this way begin to expand spontaneously in from fifteen minutes to five hours, indicating that the eye extract has lost its effectiveness. Contraction can be induced again by the addition of more eye extract. This cycle can be repeated many times with the same preparation.

Of the many experiments performed it was found that chromatophores attached to pieces of isolated integument when placed in sea water retain their ability to contract for at least four hours after being removed from the shrimp. The rate of contraction, however, becomes gradually slower with time, and after two or three days in the sterile mount the chromatophore loses all power of further movement. The eye stalks of *Crangon*

were found to be as effective as those of Palaemonetes in producing rapid pigment contraction in either animal.

It is evident that the substance produced in the eye stalks of crustaceans causing the contraction of chromatophores has the properties of a hormone in that it is interspecific, and retains potency after long periods of desiccation as in the case of vertebrate endocrine organs, and also after being subjected to boiling. The remarkable increase in efficiency as a chromatophore-contracting agent in the latter case is laid to a further separation from other substances than is possible when the entire organs are merely ground in sea water.

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THE CORRELATION BETWEEN TANNING AND UNEXPOSED SKIN COLOR AS RECORDED BY THE COLOR TOP[1]

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Communicated March 28, 1931

Workers who have dealt with the subject of skin color in field investigations have often suspected the existence of some definite connection between the amount of pigment in the normal, unexposed skin and the degree of change upon exposure, but heretofore this relation has not been quantitatively demonstrated.

During recent field studies among the Indians of California and Arizona my interest in this problem became aroused and I took advantage of the opportunity to make color readings on both the exposed and unexposed skin of one hundred and sixty-seven individuals. These determinations were made by the color top method which gives quantitative results amenable to statistical analysis.[2] Briefly, this method utilizes the principle of the color wheel in which different colors mounted on a disc will blend into one shade when the disc is rotated at sufficient speed. The four colors used in skin color determinations are black, red, yellow and white. Papers of these colors are mounted on a disc in such a manner that the proportion of each to the total circumference can be varied at

will. By changing these proportions, it is possible to obtain a very close approximation to any shade of skin when the colors blend on the rotating disc. The circumference of the latter is taken as one hundred per cent and the proportions of the four colors making up its totality are read as per cents of the whole. Following usual practice, the black is indicated by the letter N while the red, yellow and white elements are designated by R, Y and W, respectively.

The hundred and sixty-seven individuals tested were chosen with a great deal of care in order that the exact blood affiliations might be known. This has greatest significance in the paper referred to in the footnote to the present title and is only important here in indicating a high variability within the group as the tested individuals ranged from full-blood Indian to one-quarter blood. By reason of this high variability the correlations to be discussed between unexposed skin color and degree of tanning are relatively low in comparison to those which might be expected under controlled conditions, although the actual coefficients are surprisingly high.

In determining these correlations, the reading of each of the four colors for the unexposed skin was taken as one variable. The other variable was the difference between these readings and those for the exposed skin on the same individual. In the total group of one hundred and sixty-seven persons of both sexes the correlation coefficients between the readings for the unexposed skin color and the degree of tanning were as follows for each color:

$$N = -0.66$$
$$R = -0.77$$
$$Y = +0.69$$
$$W = +0.71$$

The variability in the exposed skin color of the eighty males within the group is considerably less than that of the females. Presumably this is because males are more frequently out of doors and, compared with the females, the amount of exposure they receive is more constant. At any rate, if the correlations between unexposed skin color and, amount of tanning are calculated for the males alone the coefficients become perceptibly higher than for the group as a whole. For males only these coefficients are:

$$N = -0.81$$
$$R = -0.94$$
$$Y = +0.77$$
$$W = +0.74$$

Both sets of figures force the conclusion that there exists a high relation between normal unexposed skin color and the degree of color change

produced by exposure. This correlation is negative in the case of the N and R elements and positive for the Y and W colors. This is to say, the greater the proportion of black and red in the readings for the unexposed skin, the less will be the amount of change upon exposure and the larger the proportion of yellow and white, the greater will be the amount of tanning.

These conclusions are of interest in a number of ways but are perhaps of greatest significance in pointing to a practical application of this relation in the field of radiation therapeutics. It is obvious from a comparison of the coefficients for the total group and those for males only, that a certain amount of decrease in variability increases the value of the correlation coefficients. As these results are based entirely on field observations it appears legitimate to suppose that the coefficients will be still higher, perhaps of a value above 0.90, in an experimental group where the amount of exposure and other variables could be controlled. Since coefficients of this order furnish a high degree of predictability, it seems that the construction of "exposure indices" for ultra-violet light therapy is quite feasible, particularly in the treatment of rickets where the band of frequencies which is most effective is also that which produces tanning.

It appears very probable that the effective dosage of ultra-violet light in such treatments is not an arbitrary quantity but is conditioned by the amount of pigment already present in the normal unexposed skin. If this is true, the desirability of gauging the exposure to the normal skin color is obvious and in view of the foregoing it seems likely that an "exposure index" for any given skin color could be developed for use in the medical application of ultra-violet therapy. In general terms this means that the darker the skin in N and R elements and the less the proportion of Y and W, the greater will be the required effective dosage of the ultra-violet bands which produce tanning.

[1] A more complete discussion of this problem together with additional data on the diagnostic efficiency of the four colors used in the color top and their relative variability among full-blood, three-quarter blood, half-blood and one-quarter blood Indians will appear in the April-June, 1931, issue of the *Am. J. Phys. Anthrop.*

[2] The technique of color top measurements of skin color is described by T. W. Todd and L. Van Gorder, "The Quantitative Determination of Black Pigmentation in the Skin of the American Negro," *Am. J. Phys. Anthrop.*, Wash., **4**, 239–260 (1921).

The general method described in this reference was followed in the present instance except that the color disc was mechanically rotated. A description of this latter point will be found in the author's paper, "The Relation between Skin Color and Tanning," to-appear in the April-June, 1931, issue of the *Am. J. Phys. Anthrop.*

STUDIES ON ELECTROKINETIC POTENTIALS. IX.

The Electrical Field of Force at Liquid–liquid Interfaces*

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DEPARTMENT OF AGRICULTURAL BIOCHEMISTRY, UNIVERSITY OF MINNESOTA

Read before the Academy April 27, 1931

Introduction.—The electrokinetic conditions at an oil-aqueous interface have been investigated by Ellis[1] and by Powis[2] for emulsions of oil-in-water by means of cataphoresis. Mooney[3] has also described some work at such an interface using cataphoresis. McBain and Williams[4] have determined the number of free electric charges on oil droplets dispersed in water and containing a small amount of cetyl sulfonic acid. This investigation was done by balancing the effect of gravity against the electric charge on the oil droplet by means of a strong electric field.

For various reasons it appeared highly desirable to us to develop a new technique for determining the electrical potential at a liquid–liquid inter-

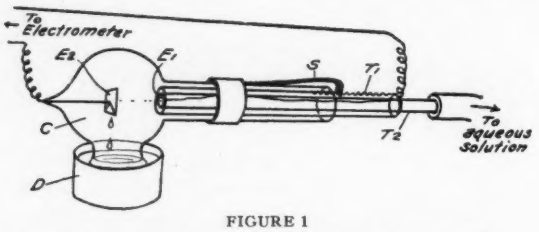

FIGURE 1

Streaming potential cell for measuring potentials at either liquid–air or liquid–liquid interfaces.

face. It is the purpose of this paper to describe a technique using the streaming potential method.

Experimental.—We made use of an apparatus which was developed by William McKinley Martin for measuring the spray potentials at a liquid–air interface. Thanks are due Dr. Martin, who permitted us to use his apparatus in advance of publication of his data. This apparatus is shown in figure 1.

The distance between the two platinum electrodes (E_1) and (E_2) was regulated by means of the spring clip which fitted into the grooves in the glass tubing (T_1). The aqueous salt solution was contained in a liter Pyrex suction flask and connected to the glass tube (T_2) by means of a short rubber tube. Special care was exercised to thoroughly clean the rubber tubing before using it. The salt solution was forced out of the flask into tube (T_2) by means of air pressure which was measured by

means of a mercury manometer. From tube (T_2) the liquid passed out of a pinhole in the platinum electrode (E_1) and then through the oil contained in the cavity (C) held above the dish (D) of salt solution. The stream of salt solution then struck the electrode (E_2), imparting an electric charge to it. The solution fell through the oil in drops into the dish (D). The wires leading from the electrodes (E_1) and (E_2) were brought out to a quadrant electrometer and the potential measured, using the electrometer as a null instrument as has been described by Bull and Gortner.[4] The mathematical considerations whereby the electrokinetic potential at the interface can be calculated have been discussed in detail in earlier papers (Briggs,[6] Bull and Gortner[5]), and we have used in the present study this formula:

$$\zeta = \frac{4\pi\eta\kappa H}{P\epsilon}$$

where ζ = the potential at the interface.

η = coefficient of viscosity of the liquid being streamed.

κ = specific conductivity of the liquid being streamed.

H = observed e. m. f.

P = hydrostatic pressure under which the liquid is forced through the opening in the electrode.

ϵ = dielectric constant of the liquid being streamed.

All values being in electrostatic units.

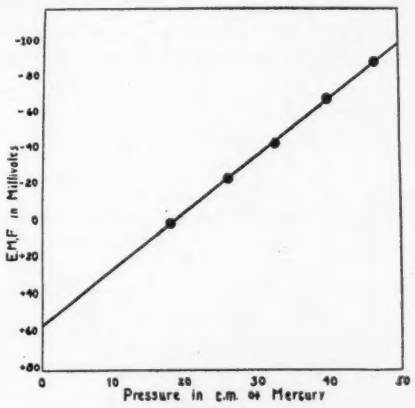

FIGURE 2

Relation between the e. m. f. developed across the electrodes of the streaming potential cell and the hydrostatic pressure under which streaming is induced. Distance between electrodes 5.6 mm.

Our present data are reported in terms of $\kappa H/P$ which is directly proportional to the ζ-potential, since all other factors are constant in the series of determinations. As the amount of electricity derived from the oil-water interface was quite small the electrometer was very sensitive to external electrical fields and the whole system had to be carefully shielded.

The only oil used in the experiments under discussion was "Nujol," a colorless paraffin oil prepared for medicinal purposes. The salt solutions were NaCl, $CaCl_2$, $ThCl_4$ and sodium stearate. They were all made up in stock solutions which were $N/500$. Dilutions were made from these

solutions. The NaCl was dried and made up to $N/500$ directly. An approximately $N/10$ solution of $CaCl_2$ was made and carefully analyzed for its calcium content. This solution was then diluted to $N/500$. The $ThCl_4$ was weighed out and made up to $N/500$. The sodium stearate solution was obtained by weighing out pure stearic acid and adding sufficient $N/10$ NaOH to exactly neutralize the acid. This was then diluted to $N/500$.

Inasmuch as the surface of the salt solution exposed to the oil was quite small it was considered proper to neglect the surface conductance. Accordingly, all conductivity data reported in this paper are those of the solutions in bulk. The conductivity was determined in a conductivity cell described in detail by Washburn[7] for specific conductances between 10^{-6} and 10^{-4} reciprocal ohms. The resistance was determined with a

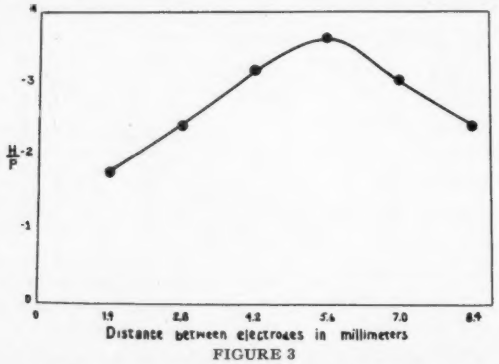

FIGURE 3

The ratio of the e. m. f. to pressure in the streaming potential cell plotted against distance between the electrodes.

Leeds and Northrup Alternating Current Galvanometer. The cell constant was determined both with $N/10$ and $N/100$ KCl and using the Kohlrausch values. Head phones tuned to 1000 cycle vibration were used to determine the cell constant.

Since it was difficult, if not impossible, to determine the zero reading of the quadrant electrometer at zero pressure, i.e., when no liquid was flowing, due to the tremendous resistance of the paraffin oil, it was necessary to take the zero point of the electrometer when the liquid was under about 15 mm. of mercury pressure. Successive readings were taken as the pressure was increased and the results plotted. The best straight line was drawn through the points and extrapolated to zero pressure and the polarization determined and this value added to all the other potential readings.

Results.—It is of interest that within wide limits a straight line relationship was found between the pressure imposed on the liquid and the observed potential. This is shown in figure 2.

The effect of varying the distance between the electrodes was investigated. This is shown in figure 3. A similar behavior was found by Zwaardemaker[3] for spray potentials, i.e., aqueous solutions sprayed through air.

No systematic investigation of the effect of the size of the aperture in the platinum electrode was made but preliminary measurement indicated that as the size of the hole was increased the maximum H/P value was obtained at a smaller distance between the electrodes.

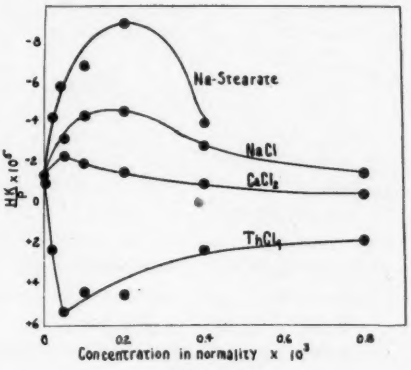

FIGURE 4

Electrokinetic potential curves for paraffin oil–aqueous solution interfaces as measured by streaming potential.

The results obtained were reproducible within about 6%.

No systematic investigation of the effect of temperature variation was conducted but the data in table 1 will give some idea of the magnitude of the temperature coefficient.

TABLE 1

EFFECT OF TEMPERATURE ON POTENTIAL AT OIL-WATER INTERFACE

T	H/P
22.5°	2.81
26°	2.00

The effect of NaCl, $CaCl_2$, $ThCl_4$ and sodium stearate at various concentrations was determined. The electrodes were 5.6 mm. apart. The data are given in tables 2 and 5 and graphed in figure 4. H is the observed streaming potential and is expressed in millivolts. P is the pressure

TABLE 2

THE EFFECT OF NaCl ON THE ELECTRICAL POTENTIAL AT AN AQUEOUS-OIL INTERFACE

CONC. × 10^3	H/P	$\kappa \times 10^6$ OHMS^{-1}	$\frac{H\kappa}{P} \times 10^6$
0.00	−8.33	1.77	−1.47
0.05	−4.24	7.78	−3.30
0.10	−3.12	14.22	−4.44
0.20	−1.72	26.96	−4.64
0.40	−0.76	51.81	−3.94
0.80	−0.15	101.64	−1.57

under which the solution is being streamed and is expressed in centimeters of mercury.

TABLE 3

THE EFFECT OF $CaCl_2$ ON THE ELECTRICAL POTENTIAL AT AN AQUEOUS-OIL INTERFACE

CONC. $\times 10^3$	H/P	$\kappa \times 10^6$ OHMS^{-1}	$\frac{H\kappa}{P} \times 10^5$
0.05	2.59	8.96	−2.39
0.10	1.29	16.02	−2.07
0.20	0.56	29.90	−1.66
0.40	0.19	56.0	−1.06
0.80	0.04	109.0	−0.47

TABLE 4

THE EFFECT OF $ThCl_4$ ON THE ELECTRICAL POTENTIAL AT AN AQUEOUS-OIL INTERFACE

CONC. $\times 10^3$	H/P	$\kappa \times 10^6$ OHMS^{-1}	$\frac{H\kappa}{P} \times 10^5$
0.004	−4.00	2.84	−1.14
0.020	+5.06	4.39	+2.22
0.050	+5.15	10.18	+5.24
0.100	+2.05	21.12	+4.33
0.200	+1.05	42.38	+4.45
0.400	+0.35	64.17	+2.25
0.800	+0.15	119.59	+1.82

TABLE 5

THE EFFECT OF SODIUM STEARATE ON THE ELECTRICAL CONDITIONS AT AN AQUEOUS-OIL INTERFACE

CONC. $\times 10^2$	H/P	$\kappa \times 10^6$ OHMS^{-1}	$\frac{H\kappa}{P} \times 10^5$
0.02	15.05	2.91	−4.38
0.04	14.50	4.12	−5.97
0.08	9.50	7.36	−6.99
0.20	5.18	17.70	−9.17
0.40	1.20	33.93	−4.07

Discussion.—It is undoubtedly true that in this series of determinations we have not been measuring the true zeta potential but only a part of it. For example, in figure 3, showing the effect of the distance between the electrodes, the maximum potential is obtained at 5.6 mm. In ordinary streaming potential work the observed potential is quite independent of the distance between the electrodes. This change of the potential with the distance is due probably to several causes, one of the most important of which is the movement of the oil surface along with that of the aqueous solution. This fact also probably accounts for the fairly high temperature coefficient since the observed potential would depend upon the viscosity of both the oil and the water. The mathematical analysis of this situation would probably be complicated. It would have to take into account the shape and size of the containing vessel unless the volume

of oil was taken very large so that the effect of the walls of the vessel could be neglected.

Surface tension measurements in conjunction with these studies should be of considerable interest. We know that at the interface the following relation should hold

$$\left(\frac{\partial \gamma}{\partial E}\right)_A = -q,$$

where γ is the interfacial tension, E is the potential difference across the Helmholtz double layer and q is the charge per unit area. If the surface tension be plotted against the potential difference a maximum should be found when $q = 0$. The work of Ellis[1] and of Harkins and Humphrey[9] indicating that salts produce very little change in the interfacial tension between oil and water is hard to understand in light of the present work.

The fact that sodium stearate increased the potential so highly is probably due to the fact that there was a tendency for the negative stearate ion to become oriented in the oil layer, thus imparting a high negative charge to the oil side of the interface. It is our intention to continue the work with the soaps of other fatty acids.

It is of interest to note that the form of our curves closely resembles those reported by Briggs[6] and Bull and Gortner[5] for cellulose-aqueous solution systems, and Kruyt[10,11] and Freundlich[12] for glass-aqueous-solution interfaces.

Summary.—1. A new apparatus has been designed for measuring the electrical potential at a liquid–liquid interface.

2. The effect of changing the distances between the electrodes has been investigated. A position is found which gives a maximum streaming potential.

3. The temperature coefficient is found to be appreciable.

4. The potentials with solutions of NaCl, $CaCl_2$, $ThCl_4$ and sodium stearate against Nujol have been determined. $ThCl_4$ was found to reverse the potential at 0.005×10^{-3} normal. Sodium stearate tremendously increases the potential.

5. The electrokinetic potential curves at an oil-aqueous solution interface resemble closely electrokinetic potential curves at cellulose-aqueous solution interfaces, glass-aqueous solution interfaces, etc.

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REVERSIBLE COAGULATION IN LIVING TISSUE. III[1]

BY WILDER D. BANCROFT AND G. H. RICHTER[2]

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Read before the Academy April 28, 1931

One function of sodium thiocyanate in living organisms is to increase the dispersion of proteins. That is why it alleviates all troubles due to reversible coagulation of proteins. Borg[3] gave 2–10 grains of potassium thiocyanate [it should have been sodium thiocyanate] three times a day for one to four weeks to a group of patients suffering from high blood pressure. Quite apart from the change in blood pressure, thirteen developed unspecified unpleasant complications which disappeared within a few days after the drug was discontinued. Toxic psychoses developed in four patients, with disorientation, hallucinations of sight and hearing, mania, confusion, and ideas of persecution, singly or in combination. They lasted only from five to seven days after the drug was stopped. These occurrences were all with patients to whom it had been necessary to give large doses.

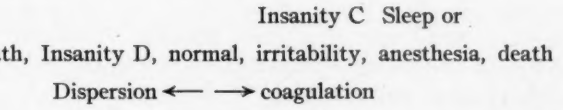
This means that one form of insanity can be brought on by administration of too much of a dispersing agent. We will call this dispersion insanity or Insanity D. This cannot be the only form of insanity, because hysteria often goes over into insanity and this must be due to a coagulation of the brain colloids. We will call this type coagulation insanity or Insanity C. Shipwrecked sailors in boats often get hallucinations and go insane before jumping overboard or before drinking salt water. This is also a coagulation insanity.

There are therefore at least two types of insanity, in one of which the brain colloids remain more or less permanently in the stage of irritability resulting from coagulation, and in the other of which the brain colloids are more or less permanently in a state of over-peptization. These two types can be covered by the statement that insanity is characterized by a more or less permanent, abnormal, degree of dispersion of the brain

colloids. We are not yet in a position to say what degree of coagulation or over-peptization is characteristic of insanity, except that it must stop short of sleep for Insanity C and must stop short of collapse for Insanity D. It is not claimed that this definition covers all cases of insanity; but it offers a basis of classification which seems likely to be helpful and which seems to cover what might be called the normal types of insanity, where there are no lesions due to obviously abnormal causes.

Most of us have been conscious of being temporarily insane at times when waking up in the night, especially if waked suddenly. There are no data to show whether all people always pass through a brief stage of insanity on going to sleep and on waking up, or whether the insanity stage is not usually in the regular sequence but gets shunted in on special occasions. What one decides will depend largely on what one feels about dreams. They are certainly abnormal thinking and the dreams arising from opium or hashish do not differ in anything except persistence from the hallucinations of insanity. The physiologist does not like to call dreams temporary insanity. They certainly do not constitute legal insanity and the physiologist does not like the term temporary insanity, though this seems to us a perfectly good concept which should not be left to lawyers in criminal cases.

We can represent our present knowledge graphically as follows, dispersion being at the left and coagulation at the right:



It can be left open whether Insanity C always comes in the midst of irritability or only at times. If the former is true, then the region of insanity is ordinarily passed through so rapidly in the case of normal people that they are not conscious of it. In the case of insane people, the insanity stage covers a wide range and the patient does not ordinarily pass out of it to the left at all. It is the reverse of what happens with morphine and caffeine, both alkaloids. Morphine carries the patient rapidly through the irritable stage into sleep and anesthesia. Caffeine takes the patient normally only to the irritable and consequently wakeful stage.

If Insanity C is a coagulation phenomenon, addition of a coagulating agent short of sleep or anesthesia should be bad for the patient, while he or she ought to improve when a peptizing agent, such as sodium bromide, is given. Sodium thiocyanate would be better than sodium bromide; but the data are lacking for it or are unknown to us. It is well-known

that coffee is bad for most insane patients and this undoubtedly means those suffering from Insanity C. Wright[4] has obtained some remarkable results with insane patients by administering 100–300 grains of sodium bromide per day. In regard to one patient he says: "For about four years she was kept in a room and much of the time she was kept in bed. When allowed in the day-room she made impulsive assaults on other patients and employees. She was regarded as dangerous from the fact that she so often attempted to bite people, especially on their ears. In three instances she succeeded, each patient losing part of an ear. Treatment was begun on September 24, 1924. She gradually improved. On November 5 she helped make beds and ran a floor brush. Since that date she has received treatment whenever she has shown a tendency to become irritable. As a result she has become industrious, and helps with the ward work. She has made no assaults for several months past."

One of the nurses said: "Before these patients were treated we had to struggle with them every morning to get them bathed and dressed. Then when one was dressed and put in the day room, her anger having been aroused because of the attention necessarily given her, a fight with another patient usually resulted and the combatants had to be separated before further work could be done. This was a frequent occurrence every morning. By the time the patients were finally bathed and dressed, we were all tired out from struggling with them before the day's work had begun."

Another nurse stated: "Before the treatment was begun it took four or five of us to bathe and dress these patients. Yesterday morning (i.e., some months after treatment was instituted) I supervised the bathing and dressing of these patients alone."

About twenty-five per cent of the patients were classed as unimproved; but Wright does not distinguish two types of insanity and consequently one does not know whether the failures were due to treating the wrong type of patient or to some other cause. In fact, the only way that we can tell that any of Wright's patients suffered from Insanity C is that those are the ones who should be benefited by such a treatment. That is reasoning in a circle to some extent. Wright does state, however, that "most of the failures have occurred in states of apathy," and we should expect these to be suffering from Insanity D. Wright also says that "in the administration of this drug [sodium bromide] in large doses, constant careful observation on the part of both nurses and physicians of each symptom produced by the drug is very necessary in order to prevent the development of distressing symptoms. Not infrequently patients quickly develop stuporous states or other evidences of a toxic condition which require prompt and energetic treatment. For this reason it is necessary to determine as accurately as possible the tolerance to the drug of each

case treated. Unless this is done the administration of the drug is not without danger."

This sounds as though Wright were dealing at times with patients suffering from Insanity D or with patients who were carried over by the large amount of bromide from Insanity C to Insanity D. It would have been easy to have distinguished experimentally between these cases. Patients with Insanity C would have been benefited by smaller doses of sodium bromide, while that would not have been the case for patients with Insanity D.

The reverse case in which patients with Insanity D are benefited by treatment with a coagulating agent has been studied at Wisconsin though not under this name. Loevenhart, Lorenz, Martin and Malone[5] have studied the effect of carbon dioxide, a coagulating agent,[6] with very striking results. "The most favorable and striking reaction occurred in those patients who had been mute and mentally inaccessible for long periods of time. In these cases, after a short period of respiratory stimulation, this inaccessibility disappeared and the catatonia passed off. A number of patients have carried on conversation.... A number of patients appeared frightened when the cerebral stimulation developed; they looked about apprehensively but became calm and at ease quite promptly when efforts were made to reassure them. In other words, they seemed to comprehend the situation correctly and, following this almost immediately, they made coherent and relevant replies to questions. In one patient who had been mute for more than six years, the efforts at speech for about two minutes resulted in a jumble of unintelligible but speech-like sounds, after which the words became distinct and a successful conversation was held....

"During the period of cerebral stimulation, the inhalation of carbon dioxide and oxygen was stopped. If no more gaseous mixture is given, the patient returns gradually to his former condition. This return is as striking as is the development of increased psychic activity. Gradually the patient's attention can no longer be held; he ceases to respond to questions: muscular tensions redevelop, if previously present, and quite like the drawing of a curtain on psychic function, the patient returns to his former stuporous condition. In some cases, during the period of stimulated mental function, the patient responded quite like a talkative psychotic person, expressing many bizarre delusions and resembling in every way rather typical psychotic patients. In one notable case there was a prolonged period of from ten to twelve minutes during which the patient maintained a comprehensive conversation without any evidence of psychosis; then quite suddenly the patient seemed to become frightened and began to express many delusions in a loud voice."

In a later paper, Lorenz[7] describes experiments which support our viewpoint in a quite remarkable manner. "It was found that cases of

catatonic stupor responded to this narcotic quite like a normal individual. That is, within 4 to 5 minutes, and before a total of 10 to 14 cc. of the solution are injected they sink into deep sleep. The muscular rigidity disappears; the reflexes are abolished; breathing becomes slow and quite shallow; the systolic blood pressure falls 30 to 40 millimeters of mercury. After an hour the blood pressure returns to its former level; the patient can then be aroused and will respond to painful stimuli. Then follows a period of what appears to be normal sleep, the duration of which is determined largely by noises or other disturbing environmental influences.

"In the stuporous catatonic cases we have seen prolonged periods of mental clearness following the state of deep narcosis. A brief account of one such case will serve to illustrate the striking change.... [The patient] had been in a state of catatonic stupor for a period of four months when she was admitted to our service and sodium amytal administered. At this time the patient showed rather extreme muscular rigidity; active negativism; her limbs, head and body in a flexed position resembling the fetal posture. She had been tube fed for over four months and voided involuntarily. Furthermore she was in a state of extreme emaciation, weighing 66 pounds.

"The patient was given $^1/_2$ gm. of sodium amytal dissolved in 10 cc. of distilled water by intravenous route. Within five minutes she was in a state of deep narcosis. The muscular rigidity had disappeared; all reflexes, including the corneal, were absent. She continued in this state of deep narcosis for about an hour and then continued at a level of unconsciousness which could be influenced by slight painful stimuli. She remained in this condition another three hours, or a total of seven [?] hours, after the time of the injection. She was then aroused by speech and she responded to conversation, asked for food and drink. She continued in this aroused mental state for a period of about four hours, when no further efforts were made to keep her awake and she then dropped into what appeared to be a natural sleep for a period of five hours, when the mutism, muscular rigidity and active negativism redeveloped slowly.

"This patient has been treated repeatedly with sodium amytal and similar reactions have been observed invariably. During this stage of mental clearness many extremely interesting thoughts have been expressed. The most striking and, in some respects, pleasant behavior has been the voluntary request for food. This patient ordered a large meal, all of which she ate with apparent relish. She drank large quantities of fluid. She expressed a wish to go to the bath room, to which she was assisted. She was found to be remarkably clear as to current events. The most trifling happenings within her possible sphere of knowledge seemed to be recorded accurately. This awareness of outside conditions was

demonstrated strikingly when she inquired as to the progress of a football game which was being played between Wisconsin and Purdue. This game was actually in progress on this Saturday afternoon when she was aroused for the first time. She inquired as to the score at about three o'clock, at which time the game was being played."

A suitably small dose of sodium amytal or other coagulating agent should have brought the patient back temporarily to normal without putting her to sleep. This was apparently not tried by Lorenz; but this gap had been filled by Berger[8] nine years before it appeared. He injected small amounts of cocaine hydrochloride into eleven patients suffering from catatonic stupor, and noted that the majority became active immediately after the first injections. The improvement did not last more than an hour or two.

Alcohol is credited with some nearly ten per cent of the mental disorders that lead to hospital incarceration. It is a coagulating agent for the brain colloids among others. In its action on the brain it first stimulates and then depresses, the depression passing into sleep, anesthesia or death, depending upon the amount taken. If taken repeatedly in considerable amounts, visual and auditory hallucinations develop and general mental confusion. The combination of these effects in various degrees will mark the person as temporarily insane. Since the initial stages of coagulation are easily reversible, it is not surprising that these cases often recover in a short time. After excessive and long-continued use of alcohol, demented states of long duration occur, frequently associated with actual damage to the nervous system (Korsakoff's disease). This is clearly a case of a difficultly reversible coagulation.

There are two phases in the action[9] of salts of lead on the brain. In low concentrations or in the initial stage of poisoning, stimulation of the brain and of the optic nerves causes hallucinations of sight and mental disturbances which resemble those of delirium tremens. The second phase is exactly what one would expect of a coagulating agent. The stage of stimulation passes into depression, during which the early symptoms of paresis appear. In more advanced stages there is actual paralysis and damage to the nervous tissue. Lead is not alone in these effects. The salts of mercury, copper or arsenic, which are coagulating agents, will cause disturbances[10] of this type.

Clevenger[11] observed a case of lead poisoning in which the symptoms of mute depression, observable in ordinary melancholia and epileptiform convulsions were present. He treated the patient with potassium iodide and in a short time the patient was discharged as fully recovered. He points out that "had the cause of this attack been unascertained, the patient would have died insane."

Indirect narcotics, such as carbon monoxide, have been known to

produce insanity. A more interesting type is that produced by lowering the pressure of oxygen in a medium that is being breathed by the subject. The exclusion of oxygen will lead to an asphyxiation narcosis; but, if the oxygen pressure is not decreased that far, an interesting series of mental reactions is observed. Such cases are important because it is recognized that aviators may become incapacitated[12] temporarily when flying at high altitudes. There is a height for each aviator above which it is not safe for him to go. The symptoms of the disturbance produced by pressures of oxygen lower than this value are: "mental confusion, leading to errors of performance; sometimes hallucinations of sight and hearing; and, in some cases, an uncontrollable desire to sing and whistle." Sodium thiocyanate should be helpful in these cases.

The general conclusions of this paper are:

1. There are two types of insanity which have not hitherto been differentiated properly by medical men. In one the mental disorder is due to over-coagulation of the brain colloids and in the other to over-peptization of them.

2. We have called the coagulation insanity Insanity C and the dispersion insanity Insanity D. Stuporous catatonia is certainly Insanity D. Manic-depressive insanity is apparently Insanity C. The evidence is contradictory in regard to catatonic excitement. Paresis produced by lead poisoning is apparently Insanity C.

3. It seems probable that there are two entirely different sets of phenomena which are now classed under catatonic excitement. In one we have a dispersion and the patient can pass to or from stuporous catatonia without passing through a normal stage. In the other we have a coagulation and the patient cannot pass to or from stuporous catatonia without passing through a normal stage.

4. Bromide or thiocyanate will carry a patient in the dispersion form of catatonic excitement into stuporous catatonia. Bromide or thiocyanate will carry a patient in the coagulation form of catatonic excitement temporarily at least into a normal stage.

5. Both dispersion and coagulation states are apparently included under dementia praecox. Since the coagulation form of catatonic excitement apparently involves deterioration, it is included at present under dementia praecox.

6. Insanity C can be helped by treatment with sodium bromide and could undoubtedly be helped still more by sodium thiocyanate.

7. Insanity D can be produced in normal people by suitable treatment with sodium thiocyanate. It can be helped by coagulating agents such as cocaine and sodium amytal. It could probably be helped by caffeine.

8. The insanity experienced by aviators at great heights is Insanity C. Sodium thiocyanate should be helpful but has apparently not been tried.

9. It is possible, though not proved, that sane people go through an insane stage on going to sleep and on waking up. If so, ordinary dreams and dreams due to opium or hashish should be classed as abnormal thinking due to temporary insanity.

10. No assumption has yet been made as to whether in catatonia, circular insanity, epilepsy, etc., the same portions are or are not affected. That will be discussed at a later time.

Our thanks are given to Dr. Seymour DeWitt Ludlum of Philadelphia, who is primarily responsible for our starting on this investigation. Our results confirm his general point of view.[13] We thank Professor H. P. Weld of Cornell University for help with regard to classification.

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A CRITIQUE OF RECENT QUANTUM THEORIES

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Part I—Their Mathematical Structure.—More than a year ago there was written by the present author[1] a critique of the new quantum theories prior to the general formulations of Jordan, of Dirac and of Weyl. Not that the latter were overlooked! On the contrary their very successes—and failures—are encouched in their mathematical reducibility to the simpler forms for physical applications. Then, too, the heuristic possibilities of the decidedly distinct, philosophical views first given justify any attempt to keep them separate. The recognition of this truth by Born, by de Broglie, by Heisenberg and by Dirac in their recent books clearly indicates that the new quantum mechanics, already "classical"

in its mathematical technique, is still speculative in its physical interpretations. In each case the author's extensions seem to have intensified his earlier feelings. At the same time we cannot help noting that several vital matters included in the critique are yet to be emphasized. Hence, this synoptic survey of it!

There is much confusion—not to mention disagreement—among modern physicists as to just what, in physics, is postulational and just what is experiential. For example, take so fundamental a concept as is expressed by Newton's second law of motion. Every interpretation of this as an identity defining force is attacked by those regarding it as an equation relating two measurable, physical quantities. What a difference! In the light of such haziness modern theories can hardly be expected to present clear outlines. And yet, here, above all, ought mathematical changes to be carefully differentiated from physical innovations. Indeed, this is the only safe support for one diving into the unexplored interior of the atom. Let us, therefore, set up the most general, mathematical scheme that will satisfy the basic needs of the new theories. Then we can later examine this for the relative merits of the various, physical particularizations without jeopardizing the value of the general scheme. In passing, we note that the very opposite of such a method is employed by Hilbert, v. Neumann and Nordheim.[2] However, their presentation is based on a probability-view of the microcosm. With such an assumption no other method is logically possible. For the physical interpretation has already been prescribed—if, indeed, one can ever speak of a statistical formulation as a description of phenomena. But one must admit also that the Hertzian (first enunciated by Goethe), prophetic promise, essential to the growth of a physical theory, cannot be born from barren, "stereotyped ignorance." Moreover, certainty about uncertainty seems too pessimistic for a science nurtured on uncertainty about certainty. So we hopefully proceed to examine the mathematical structure of the recent theories. First, we observe that its mathematical form must be purely symbolic in the manner of Dirac.[3] And what is more, its algebra must be non-commutative—the *sine qua non* of all quantum mechanics since 1925.

A Symbolic Algebra.—We shall deal with a set of terms that form a group. Terms that are capable of entering into the relations "greater than" and "less than" will be called magnitudes ($\alpha, \beta, \gamma, \ldots$). The rest of the set will be called symbols ($a, b, c, \ldots$). All the rules of ordinary algebra will be assumed to hold with the exception of the commutability of the symbols. In this connection we make the fundamental postulate that the idemsymbol be expressed as

$$I \equiv \alpha\{u, v\} \equiv \alpha(uv - vu) \qquad (1)$$

where the so-called brace-symbol $\{u, v\}$ is symmetric in the independent elements, q and p, necessary to describe dynamically the state of a system (with one degree of freedom, for simplicity). We employ the word symmetric to signify that the following relation must hold:

$$uv^2u \equiv vu^2v. \tag{2}$$

It can be easily shown by the method of *reductio ad absurdum* that this is always a necessary, though not sufficient, condition for (1) to be true. Hence, three items are to be determined solely from physical data: namely, (A) the identification of u and of v, e.g., $\{p, q\}$, $\{p^{-1}, q^{-1}\}$, $\{p^2, q^2\}$, etc., (B) a unique interpretation of q and p, e.g., as operators, as matrices, etc., (C) the specification of α. After u and v have been particularly designated, it is customary to call any other functions, $g(u, v)$ and $h(u, v)$, satisfying (1) "canonical conjugates." The recent theories agree that for (A) $u \equiv p$ and $v \equiv q$ and that for (C) $\alpha \equiv \frac{2\pi i}{h}$. Their differences regarding (B) will be considered later. It is to be noted, however, that such choices in the case of (A) are wholly arbitrary. They are more the result of historical growth than of logical necessity. And what is the determining factor of the latter? Anthropomorphic economy of thought! We mention this, not in a derogatory, but in a critical sense; not so much to stamp the past with incompleteness as to prepare the future for completeness. For in this way we understand Cousin's statement: "La critique est la vie de la science."

As a result of the form of the idemsymbol, it is found convenient to introduce the bracket-symbol (quasi-Poisson of Dirac) defined by

$$[u, v] \equiv \alpha\{u, v\} \tag{3}$$

For any x and y, rational functions of u and v, the following relation is found to hold:

$$[x, y] \equiv \alpha\{x, y\} \tag{4}$$

Consider an example, $\{p^{-1}, q^{-1}\}$.

Now $$\{p^{-1}, q^{-1}\} \equiv p^{-1}q^{-1}\{p, q\}q^{-1}p^{-1}$$

and $$[p^{-1}, q^{-1}] \equiv p^{-1}q^{-1}[p, q]q^{-1}p^{-1}$$

therefore, $$[p^{-1}, q^{-1}] \equiv \alpha\{p^{-1}, q^{-1}\}.$$

In general, the proof depends upon the reduction of $\{x, y\}$ to a linear function of $\{p, q\}$. This is always possible for x and y as rational functions. If a transcendental be defined by an infinite series composed of rational terms, the relation (4) can be extended to such. However, let us consider a case involving irrational functions, e.g., $\{p, q^{1/2}\}$.

Now $$\{p, q\} \equiv \{p, q^{1/2}\}q^{1/2} + q^{1/2}\{p, q^{1/2}\}$$

but $$\alpha\{p, q\} \equiv I.$$

If $\{p, q^{1/2}\}$ be defined as $\frac{1}{2\alpha}q^{-1/2}$, then the second of these relations is satisfied provided that the interpretation given our symbols is unique in itself, as demanded above.

Also $$[p, q] \equiv [p, q^{1/2}]q^{1/2} + q^{1/2}[p, q^{12}]$$

and $$[p, q] \equiv I.$$

If $[p, q^{1/2}]$ be defined as $\frac{1}{2}q^{-1/2}$, then our second identity is true. Therefore,

$$[p, q^{1/2}] \equiv \alpha\{p, q^{1/2}\}.$$

The arbitrariness of this method disappears when the interpretations are made. But such an identification is not always possible, as is seen below. Consider $\{p^{1/2}, q^{1/2}\}$.

Now $$\{p, q\} \equiv \{p^{1/2}, q^{1/2}\}q^{1/2}p^{1/2} + q^{1/2}\{p^{1/2}, q^{1/2}\}p^{1/2} + p^{1/2}\{p^{1/2}, q^{1/2}\}q^{1/2} + p^{1/2}q^{1/2}\{p^{1/2}, q^{1/2}\}$$

and $$\alpha\{p, q\} \equiv I.$$

It seems from inspection that there is no algebraic definition of $\{p^{1/2}, q^{1/2}\}$ which will satisfy the second relation. This means that not all functions of p and q can be subjected to the so-called quantum condition. In fine, our algebra is limited in its usage. Thus the collapse of our theoretical structure in any instance may be due to the limitations of our mathematical tools as well as to the inapplicability of our physical materials.

The inverse-symbol of any symbol of a group is determined by the idem-symbol by the following relation:

$$x^{-1}x \equiv I. \tag{5}$$

We are always confronted practically by the form of x^{-1} in terms of u and v. Modern theorists never seem to be bothered about such petty problems. (Perhaps that is one reason their theories are inevitably of limited scope—and hence, unintelligible.) In this particular case, for example, they will use x^{-1} without any thought of its meaninglessness if it be neither inherent in the algebra nor defined additionally. Of course, this does not necessarily invalidate their final result so long as it does not contain x^{-1} explicitly—fortunately. But then again, it may! The truth of this is seen in the exaggerated instance of using the inverse-symbol 0^{-1} indiscriminately without any knowledge of its nature. Hence, we believe

that the problem of determining x^{-1} in terms of the elements p and q is of prime importance. Two examples will be given to substantiate this claim. Suppose $x \equiv (ab^{1/n})$. It is found that x^{-1} cannot be expressed except formally, as $(ab)^{-1/n}$. Probably our difficulty lies in the obscurity of x. At any rate, some additional definition must be given before x^{-1} can be used. And this means that the form of x is limited—consequently, our algebra also. If, however, $x \equiv (gh)^{1/n}$, where g and h are canonical conjugates (i.e., $[g, h] \equiv I$), then x^{-1} can be determined. A different situation arises for $x \equiv (a + b)$. Here again, another definition is needed. Postulating $(1 + y)^{+m/n}$ to be an infinite series, we find that x has two distinct inverse-symbols. Therefore, there is a lack of uniqueness. What is the physical significance of this? We shall return to this point later.

Now we have exhausted the content of our symbolic algebra. So we turn from logic to the mystical domain of analogy—what mathematicians defensively call "one to one correspondence." For we notice that it is possible to express the bracket-symbol in terms of other symbols similar to ordinary derivatives. Differentiation, however, need not be defined. All that we are to understand by the notation of the differential calculus is an equivalent-symbol. For n a positive integer and x any function reduced to simple terms in g and h (canonical conjugates), relations of the following type are found to be true:

$$[g^n, x] \equiv \frac{\partial x}{\partial h} g^{n-1} + g \frac{\partial x}{\partial h} g^{n-2} + \ldots + g^{n-2} \frac{\partial x}{\partial h} g + g^{n-1} \frac{\partial x}{\partial h}$$

$$[g^{-n}, x] \equiv -(g^{-1} \frac{\partial x}{\partial h} g^{-n} + g^{-2} \frac{\partial x}{\partial h} g^{-n+1} + \ldots + g^{-n+1} \frac{\partial x}{\partial h} g^{-2} + g^{-n} \frac{\partial x}{\partial h} g^{-1}). \quad (6)$$

The possibility of this formal correspondence between the bracket-symbol and the equivalent-symbol is inherent in their natures, as is seen from the following table:

	Equivalent-Symbol	Bracket-Symbol
Element	$\frac{\partial x}{\partial x} \equiv 1$	$[g, h] \equiv I$
Sum	$\frac{\partial}{\partial x}(y + z) \equiv \frac{\partial y}{\partial x} + \frac{\partial z}{\partial x}$	$[g, y + z] \equiv [g, y] + [g, z]$
Product	$\frac{\partial}{\partial x}(yz) \equiv \frac{\partial y}{\partial x} z + y \frac{\partial z}{\partial x}$	$[g, yz] \equiv [g, y]z + y[g, z]$

This analogy can be extended to equivalent-symbols of a higher order, e.g.,

$$[g, [h, x]] \equiv [h, [g, x]]$$

i.e.,
$$-\frac{\partial^2 x}{\partial h \partial g} \equiv -\frac{\partial^2 x}{\partial g \partial h}.$$

The Problem of Canonical Conjugates.—Canonically conjugate quantities are always appearing in the new theories—symbolically. But there is a symbolism that is employed for clarification and also a symbolism that is used for concealment. Can the abstractness in this instance be of the latter kind? Can it be due to that lack of uniqueness ever seen, but never heard, in modern discussions? At any rate, one cannot deny that it is difficult to ascertain canonical conjugates in any particular case. The problem may be stated thus: Given $H(g, h)$, find $G(g, h)$ such that $[G, H] \equiv I$. A possible solution has already been outlined elsewhere,[4] but it is briefly repeated here as the basis for some critical remarks to be made later.

Observing that G can be determined only if H be a rational function, we proceed to reduce the bracket-symbol $[G, H]$ to a partial differential identity in equivalent-symbols, which is of the first order and of the first degree. If any solution of this exist, it must be contained in the solutions of the identity unrestricted as to non-commutativity. Suppose the variables are permutable. Then we have Lagrange's linear equation, which we solve in the usual manner. The so-called general integral of this equation is an arbitrary function of any two independent solutions of his subsidiary equations. We note that $H \equiv \beta$ is always one of the latter (at least for H, the ordinary Hamiltonian function). Finally we examine the arbitrary function for the restriction imposed.

So far no interpretation of the fundamental symbols has been made. Two are in usage: p and q as operators[5] or as matrices.[6] We shall consider each of these separately.

The Symbols as Operators.—Let
$$qF(Z) \equiv Z \cdot F(Z)$$
and
$$pF(Z) \equiv \frac{\alpha^{-1}\partial F(Z)}{\partial Z},$$
where p^{-1} is so chosen that always
$$pp^{-1}F(Z) \equiv p^{-1}pF(Z)$$
and where Z is not a symbol, but an ordinary, algebraic variable.

The introduction of the operator-concept extends our algebra to include all irrational functions, inasmuch as these are now defined. Moreover, it explains the generality of the interpretation of (1), in that any $\{u, v\}$ is a parametric magnitude for u and v symmetric. For example,

$\{p^2, q^2\}Z^n = 2\alpha^{-2}(2n + 1)Z^n$ and $\{p^{-1}, q^{-1}\}Z^n = \dfrac{\alpha}{n(n+1)}Z^n$. But $\{p, q\}Z^n = \alpha^{-1}Z^n$. Thus, in the first two cases we have the function Z^n multiplied by a magnitude that depends upon the parameter n; whereas, in the third instance the magnitude is independent of n. Hence, our choice of u and of v to satisfy (1) signifies mathematically the selection of one of all the possible parametric magnitudes to be independent of the parameter. This is seen more clearly in the operational interpretation of (2). This latter identity is found to exist on account of each side of the identity being the same parametric magnitude. For example, $(pq^2p)Z^n = (qp^2q)Z^n$; the result in each case is found to be $n(n+1)\alpha^{-2}Z^n$. Likewise for $(p^{-1}q^{-2}p^{-1})Z^n = (q^{-1}p^{-2}q^{-1})Z^n$; each side becomes $\dfrac{\alpha^2}{n(n+1)}Z^n$. As for the inverse-symbol, not only is a meaning assignable to $x \equiv (ab)^{1/n}$, but the reason for two series for $x \equiv (a + b)$ is made evident. If $x \equiv (a + b)$ be taken in its simplest form $(p + q)$, then the two distinct results obtained by operating the inverse-symbol of this on Z^n are as follows:

$$(1 + q^{-1}p)^{-1}q^{-1}Z^n = Z^{n-1} - \alpha^{-1}(n-1)Z^{n-3} + \alpha^{-2}(n-1)(n-3)Z^{n-5} -$$

and

$$(1 + p^{-1}q)^{-1}p^{-1}Z^n = \frac{\alpha}{n+1}Z^{n+1} - \frac{\alpha^2}{(n+1)(n+3)}Z^{n+3} + \frac{\alpha^3}{(n+1)(n+3)(n+5)Z^{n+5}} - \cdots$$

These two series have different ranges of convergence when operating on a function of Z. Thus, they are not identical; they are exclusive.

Of particular interest is an interpretation of our solution of Lagrange's linear equation. We are concerned with two identities, $[G, H] \equiv I$ and $H \equiv \beta$. The former is true for any function of Z; the latter, for one particular function. If H be the Hamiltonian form of the energy of a dynamical system, the equation satisfied by the special function is that of Schrödinger.[7] It is purely mathematical—a necessary condition for the existence of G canonically conjugate to H. The physical problem is thus reduced to the determination of α and to the assignment of boundary-conditions for the evaluation of β, the arbitrary constant appearing in the special function. To illustrate, we give fully the problem of finding the canonical conjugate to $H \equiv \dfrac{p^2}{2m} + kq$, corresponding to motion of a

particle with mass m in a uniform field specified by kq. By definition the following relation must be fulfilled:

$$-\left[\frac{p^2}{2m} + kq,\ G\right] \equiv I. \tag{7a}$$

The use of formulae of the type given in (6) reduces this to

$$-\frac{1}{2m}\left(\frac{\partial G}{\partial q}p + p\frac{\partial G}{\partial q}\right) + k\frac{\partial G}{\partial p} \equiv I.$$

Hence, for permutable variables we have as our Lagrangian equation

$$-\frac{1}{m}p\frac{\partial G}{\partial q} + k\frac{\partial G}{\partial p} = 1.$$

From which we form the subsidiary equations

$$-\frac{mdq}{p} = \frac{dp}{k} = \frac{dG}{1}.$$

Therefore,

$$G \equiv \frac{p}{k} + F(H), \tag{7b}$$

where F is an arbitrary function of H. But at the same time

$$\frac{p^2}{2m} + kq \equiv \beta, \tag{7c}$$

where β is a magnitude. It can be easily verified by substitution that the defining identity (7b) satisfies (7a). Moreover, this is true for the operation of (7a) on any function of Z. However, the restricting identity (7c) is true for operating on one particular function of Z only. We may write (7c) then

$$\left(\frac{p^2}{2m} + kq - \beta\right)\Psi = 0,$$

where

$$\Psi \equiv \Psi(Z)$$

or

$$\frac{\partial^2\Psi}{\partial Z^2} + 2m\alpha^2(kq - W)\Psi = 0,$$

where $W \equiv 2m\alpha^2\beta$. This is Schrödinger's equation.

The Symbols as Matrices.—Every associate algebra, such as ours, is equivalent to a matrix algebra.

Let

$$t \equiv \|\tau(NN)\|$$

where the elements of t are spectral terms. Hence,

$$\nu(NM) = \frac{1}{h}\left\{\tau(NN) - \tau(MM)\right\}.$$

Let

$$q \equiv \| \chi(NM)e^{2\pi i\nu(NM)T} \| \qquad i \equiv \sqrt{-1}$$

and

$$p \equiv \| \pi(NM)e^{2\pi i\nu(NM)T} \|$$

where q and p are square, Hermitian matrices (T signifies the time).

Our first observation of the matric interpretation hints of weaknesses. For the fundamental postulate (1) is not satisfied *ipso facto*. Rather is it a restriction upon the arbitrariness of the elements of the matrices q and p, because it necessitates a definite relation between them. This is particularly apparent in the extension of our mathematical structure to two degrees of freedom. The condition of independence of the coordinates specifying such a system is expressed by

$$q_1q_2 - q_2q_1 \equiv 0.$$

Actually, this relation is one of interdependence. For suppose

$$\chi_1(NK) = \gamma_{k1} + \delta_{k1}i$$

and

$$\chi_2(NK) = \gamma_{k2} + \delta_{k2}i.$$

Then it can be shown that in the simplest case (magnitudes all positive or all negative) the following relation must hold for diagonal terms:

$$\frac{\gamma_{k1}}{\gamma_{k2}} = -\frac{\delta_{k1}}{\delta_{k2}}.$$

But what does the notion of degree of freedom imply, if not independence?

The infinite order of the matrices introduces a new problem, convergence. For the elements of q^{+n} and of q^{-n} are given as infinite series of the elements of q. And these can be shown to be possibly divergent or even indeterminate. For example, in the case of the linear, harmonic oscillator q^{-1} is indefinable because its terms are the ratios of divergent series. Of course, q^{-1} may be used without reference to its form as a matrix, i.e., algebraically as a symbol. However, such a naïve confession of ignorance seems too puerilely radical for a virile science admitting only experience

as its *raison d'être*. The question of convergence permeates the matric interpretation of the symbols. In the instance of the inverse-symbol for $x \equiv (a + b)$ the convergence of the two distinct, infinite series must be considered. And yet, how can this be done if the elements themselves are indeterminate?

An additional difficulty arises in the use of irrational matrices, e.g., $q^{1/2}$. By the extension of a proof, due to Frobenius, one can show that there is no limit to the possible number of latent roots of $q^{1/2}$. Therefore, $q^{1/2}$ is not uniquely defined. If the number of possibilities were finite, one might be able to describe this as a degeneracy analogous to the proper functions which, though different, all exist for the same quantum state on Schrödinger's theory. But the infinite number compels us again to seek the meaning of an operation in the meaningless symbols themselves.

A simple interpretation of the problem of canonical conjugates is suggested by the use of the symbols as matrices. The identity, $[G, H] \equiv I$, is true for any matrix H; the identity, $H \equiv \beta$, specifies a particular, diagonal matrix. If H be the Hamiltonian function, then Bohr's frequency condition follows upon the identification of t and β (except for a constant factor). However, this involves the introduction of Hamilton's canonical equations of motion—corresponding formally to the setting up of boundary conditions for Schrödinger's equation. Seeing that our solution of the problem of canonical conjugates is not reasoned, only reasonable, we offer this interpretation of it soberly.

In addition to the weaknesses mentioned above there are two others of great importance: the inapplicability of the matrices to cyclic coordinates and the tediousness of calculating matric elements. Hence, we conclude that the operational interpretation of the mathematical structure of the new quantum theories is physically and, above all, logically preferable to the matric one. And what more reliable compass in a storm of ideas is there than rigorous thinking?

May I add a note of appreciation for the kind encouragement and helpful suggestions given by Professors Leigh Page of Yale University and R. Bruce Lindsay of Brown University during the writing of the original critique! And I am again grateful to the latter for his careful criticism of this particular article.

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DISSIPATIVE DYNAMICAL SYSTEMS. I.

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1. As a first approximation to physical reality, the configuration of certain physical systems, such as: the motion of a set of point masses, considered by Rayleigh;[1] or the flow of electricity in ideal electric networks, as treated by Maxwell[2] and others, may be formulated analytically in terms of a system of linear differential equations of the second order. Many theoretical questions which arise from still more ideal dynamical systems which physically may be called conservative, have been investigated by Birkhoff[3] and others. It is the purpose of the present paper to define analytically the types of dynamical systems whose configuration is given by the previously mentioned set of equations, and to establish certain facts concerning the existence of algebraic variational principles for dissipative dynamical systems. In subsequent communications certain differential topological aspects of dissipative dynamical systems and their application to the theory of electrical networks will be considered.

2. In order to facilitate the precise definition of the types of dynamical systems that are to be considered, it will be convenient to review the formulation of a general dynamical system of point masses as given by Rayleigh.[1] The equations of motion of such a system are:

$$a_{ij}\ddot{Q}_j + b_{ij}\dot{Q}_j + c_{ij}Q_j = Q_i(t) \qquad i, j = 1, \ldots n \tag{2.1}$$

where a_{ij}, b_{ij}, c_{ij} are functions of class C' on a segment γ of the t axis, and where the following symmetric properties exist between the coefficients:

$$a_{ij} \equiv a_{ji},\ b_{ij} \equiv b_{ji},\ c_{ij} \equiv c_{ji},\ \text{and}\ |a_{ij}| \not\equiv 0^*$$

physically: a_{ij} are masses, b_{ij} dissipation coefficients, and c_{ij} elastic coefficients.

If equations 2.1 are multiplied by $\dot{Q}_i$ the so-called equations of activity[4] are obtained.

$$a_{ij}\ddot{Q}_j\dot{Q}_i + b_{ij}\dot{Q}_j\dot{Q}_i + c_{ij}Q_j\dot{Q}_i = Q_i\dot{Q}_i \tag{2.2}$$

where $i, j = 1, \ldots, n$.

If the following energy functions are defined:

* The usual summation convention will be hereinafter adopted; i.e., a repeated subscript means a finite summation with respect to that letter.

$$\text{Kinetic Energy: } T = \int_0^t a_{ij}\,\ddot{Q}_j\,\dot{Q}_i\,dt$$

$$\text{Potential Energy: } U = \int_0^t c_{ij}\,Q_j\,\dot{Q}_i\,dt \tag{2.3}$$

$$\text{Dissipation Function: } F = b_{ij}\,\dot{Q}_j\,\dot{Q}_i$$

equations 2.1 and 2.2 can be reduced to the following canonical forms, respectively:

$$\frac{d}{dt}\frac{\partial(T+U)}{\partial\dot{Q}_i} + \frac{\partial F}{\partial\dot{Q}_i} = Q_i \tag{2.4}$$

$$\frac{d}{dt}(T+U) + F = Q_i\,\dot{Q}_i. \tag{2.5}$$

Equation 2.5 can be considered as a formulation of the principle of conservation of energy, where the term $Q_i\,\dot{Q}_i$ may be regarded as the rate at which energy is supplied to the system from external sources.

3. Definition: *A linear dynamical system* has the property that its equations of motion and activity are given by the canonical forms 2.4 and 2.5. It is convenient to classify further linear dynamical systems as follows:

Type I. *A conservative linear dynamical system* has the property that $F \equiv 0$.

Type II. *A dissipative linear dynamical system* has the property that $F \not\equiv 0$.

4. Variational Principles:

Classically, it has been of formal interest to establish certain variational principles which give as a necessary consequence the equations of motion of linear dynamical systems. The question naturally arises, for what types of linear dynamical systems does such a principle exist? The answer to this question follows from certain recent results on the inverse problem of the calculus of variations by Davis[5] and Morse.[6]

The general form of a variational principle is to set up an integral of the form,

$$I = \int_{t_1}^{t_2} f_i(t,\, Q_i,\, Q_j,\, \dot{Q}_i,\, \dot{Q}_j)dt \tag{4.1}$$

whose Euler equations are the equations of motion of the dynamical system under consideration. Usually the integrand, f_i, is expressed in terms of the energy functions, 2.3. Well-known principles of this type are the Principle of Least Action and Hamilton's Principle.

The following theorem due to Davis[5] will be used to establish the existence of a variational principle for the different types of linear dynamical systems:

If a given system of differential equations

$$H_i(t, Q_i, Q_j, \dot{Q}_i, \dot{Q}_j, \ddot{Q}_i, \ddot{Q}_j) = 0 \quad i, j = 1, \ldots, n$$

is to be the system of differential equations of the solutions of the problem of minimizing the integral, I, of the type indicated above, then their equations of variation must be a self-adjoint system along every curve $Q_i = Q_i(t)$.

Davis[5] and Morse[6] also show that necessary and sufficient conditions for the self-adjoint requirement are, using the system of equations 2.1:

$$\begin{aligned} a_{ij} &\equiv a_{ji} \\ b_{ij} + b_{ji} &\equiv 2\dot{a}_{ij} \\ \ddot{a}_{ij} - \dot{b}_{ij} &\equiv c_{ji} - c_{ij}. \end{aligned} \tag{4.2}$$

A linear dynamical system of type I will now be considered. In this case the requirement, that $F \equiv 0$, yields the result that $b_{ij} \equiv 0$. The relations 4.2 becomes in this case:

$$\begin{aligned} a_{ij} &\equiv a_{ji} \\ 0 &\equiv 2\dot{a}_{ij} \\ c_{ij} &\equiv c_{ji} \end{aligned} \tag{4.3}$$

From this result it is at once evident that a variational principle exists if and only if $a_{ij} \equiv$ constant. That variational principles for a system of type I exist is, of course, well known. The following theorem follows at once:

THEOREM I. *The equations of motion of a conservative linear dynamical system are given by a variational principle if and only if the masses of the system are constant.*

If a linear dynamical system of type II is considered, the relations 4.2 become by the use of the symmetric properties of the coefficients given in 2.1:

$$\begin{aligned} a_{ij} &\equiv a_{ji} \\ b_{ij} &\equiv \dot{a}_{ij}. \end{aligned} \tag{4.4}$$

The theorem which follows this is:

THEOREM II. *The equations of motion of a dissipative linear dynamical system are given by a variational principle if and only if the dissipation coefficients are identically equal to the rates of change of the corresponding masses.*

This result has the physical interpretation of connecting the mass of the system and the coefficient of dissipation of the system. If the mass of the system is a monotonically increasing function of time the dissipation function would be positive, and the system would lose energy. If the mass of the system decreases monotonically with time, the system would gain energy. If the mass of the system is an oscillatory function of time or a function of time whose first derivative is not always of one sign, several possibilities for the net gain or loss of energy by the system exist:

If a particular epoch, $t_1 \leq t \leq t_2$ be considered, the time-average rate of dissipation of energy will be given by:

$$I = \frac{1}{t_2 - t_1} \int_{t_1}^{t_2} F dt \tag{4.5}$$

If $I = 0$, the system will have no net energy loss during this epoch.

If $I > 0$ or $I < 0$ the system will have an average loss or gain of energy during this epoch.

A special case of a system of type II of particular physical importance is that in which the equations of motion 2.1 have constant coefficients. Now by relations 4.4, it is seen that

$$b_{ij} \equiv 0 \tag{4.6}$$

but this violates our hypothesis that $b_{ij} \not\equiv 0$.

Hence:

COROLLARY: *The equations of motion of a dissipative linear dynamical system with constant coefficients are not given by a variational principle.*

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HAMILTONIAN SYSTEMS AND TRANSFORMATIONS IN HILBERT SPACE

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In recent years the theory of Hilbert space and its linear transformations has come into prominence.[1] It has been recognized to an increasing extent that many of the most important departments of mathematical physics can be subsumed under this theory. In classical physics, for example in those phenomena which are governed by linear conditions—linear differential or integral equations and the like, in those relating to harmonic analysis, and in many phenomena due to the operation of the laws of chance, the essential rôle is played by certain linear transformations in Hilbert space. And the importance of the theory in quantum mechanics is known to all. It is the object of this note to outline certain investigations of our own in which the domain of this theory has been extended in such a way as to include classical Hamiltonian mechanics, or, more generally, systems defining a steady n-dimensional flow of a fluid of positive density.

Consider the dynamical system of n degrees of freedom, the canonical equations of which are formed from the Hamiltonian $H(q, p) = H(q_1, \ldots, q_n, p_1, \ldots, p_n)$, which we will assume to be single-valued, real, and analytic in a certain $2n$-dimensional region R of the real qp-space. The solutions, or equations of motion, are $q_k = f_k(q^\circ, p^\circ, t)$, $p_k = g_k(q^\circ, p^\circ, t)$, $(k = 1, \ldots, n)$, these functions being single-valued, real and analytic for all (q°, p°) in R and for t in a real interval containing $t = 0$ dependent on (q°, p°). It is shown that the transformation $S_t: (q^\circ, p^\circ) \longrightarrow (q, p)$ defined by these equations for suitably restricted t has the formal properties: $S_{t_1}S_{t_2} = S_{t_1 + t_2}$, $S_0 = I$. The system admits the "integral of energy" $H(q, p) = \text{const.}$; hence, if Ω denote a variety $H(q, p) = C$ of points of R, a path curve of S_t having one point on Ω will remain on Ω as long as the curve remains in R. We shall assume that C is such that this is the case for all values of t; this will be the situation, for example, if Ω consists of a closed set of interior points of R. It is shown that under these conditions f_k and g_k are analytic for all (q°, p°) on Ω and for $-\infty < t < +\infty$, so that S_t effectuates a one-parameter group of analytic automorphisms of Ω. Furthermore, S_t leaves invariant the value of a certain integral $\int \rho d\omega$ taken over an arbitrary region of Ω; here, ρ is a positive, single-valued, analytic function on Ω. This is a consequence of the fact that $\int dq_1 \ldots dq_n, dp_1 \ldots dp_n$ is an integral invariant of the system. In the special case where there are m further integrals $F_j(q, p) = C_j$ of the system,

we take Ω as the $(2n - m - 1)$-dimensional locus in R of these equations together with $H(q, p) = C$; but there is no further change to be made in the case treated above.

The starting point of our investigation is the N-dimensional variety Ω and the group of automorphisms S_t having the positive integral invariant $\int \rho d\omega$, and these are considered without reference to the problem which gave them origin. Let $\varphi = \varphi(A)$ be a complex-valued function of the point A of Ω, restricted only as follows: (i) φ is single-valued; (ii) φ is measurable; (iii) the Lebesgue integrals $\int_\Omega \rho|\varphi|d\omega$ and $\int_\Omega \rho|\varphi|^2 d\omega$ are finite. The totality of such functions φ constitutes the aggregate of points of a Hilbert space $\mathfrak{H}$: the metric of which is determined by the "inner product" $(\varphi, \psi) = \int_\Omega \rho\varphi\bar{\psi}d\omega$.

Let the transformation U_t of the "points" φ of $\mathfrak{H}$ be defined by $U_t\varphi(A) = \varphi(S_tA)$. This transformation is evidently defined for all φ of $\mathfrak{H}$ and is continuous in φ; and it is defined and continuous for all real t. The kinematical interpretation of U_t is immediately obvious: If t represents the time, S_t specifies the steady flow of a fluid of density ρ occupying the space Ω; and if the values of $\varphi(A)$ be regarded as being attached to the respective points A of the fluid when $t = 0$, in the course of the flow these values will be carried into those of the function $U_{-t}\varphi(A)$. Thus, $U_t\varphi$ has at A the value which φ has at the point S_tA into which A flows after the lapse of the time t.

The transformation U_t is unitary, that is, it is a one to one transformation of $\mathfrak{H}$ into itself which is linear:

$$\begin{aligned} U_t[a\varphi(A) + b\psi(A)] &= a\varphi(S_tA) + b\psi(S_tA) \\ &= aU_t\varphi(A) + bU_t\psi(A) \end{aligned}$$

and such that $(U_t\varphi, U_t\psi) = (\varphi, \psi)$. This last is an easily established consequence of the invariance of $\int \rho d\omega$ under S_t. And since[2] U_t is a one-parameter group of unitary transformations in Hilbert space, it will have on infinitesimal generator P:

$$\left[\frac{\partial}{\partial t} U_t\varphi(A)\right]_{t=0} = iP\varphi(A),$$

$i = \sqrt{-1}$, and P is a self-adjoint linear operator defined in a set of points everywhere dense in $\mathfrak{H}$: $(P\varphi, \psi) = (\varphi, P\psi)$.

In a sufficiently small region of Ω, P may be given a simple interpretation. Let $\xi_1, \ldots, \xi_N$ be a set of Gaussian coördinates of the region, the differential equations of the flow will be $d\xi_k/dt = \Xi_k(\xi_1, \ldots, \xi_N)(k = 1, \ldots, N)$; then for any differentiable $\varphi(A) = \varphi(\xi_1, \ldots, \xi_N)$:

$$P\varphi = i\sum_{k=1}^{N} \Xi_k \frac{\partial \varphi}{\partial \xi_k}.$$

We recognize the Lie operator. The property of $\rho = \rho(\xi_1, \ldots, \xi_N)$ is expressed by the "equation of continuity"

$$\sum_{k=1}^{N} \frac{\partial(\rho \Xi_k)}{\partial \xi_k} = 0,$$

which might have been used to prove formally that P is self-adjoint.

The recent results in the spectral theory of linear operators establish the existence of a "canonical resolution of the identity" E_l corresponding with U_t, which consists of a family of self-adjoint operators defined throughout $\mathfrak{H}$, with the properties that

$$E_{-\infty} = 0, \quad E_{\infty} = I, \quad E_l E_h = E_h E_l = E_h, \text{ when } h \leqq l \ (1).$$

This E_l effectuates the spectral resolution of U_t and P:

$$U_t\varphi = \int_{-\infty}^{\infty} e^{itl}\, dE_l\varphi \ (2), \quad P\varphi = \int_{-\infty}^{\infty} l\, dE_l\varphi.$$

These are Lebesgue-Stieltjes integrals and they exist in the sense of convergence in the mean. Thus, e.g.,

$$\int_{\Omega} \rho \Big| \sum_{j=1}^{J} e^{itl_j} (E_{l_j}\varphi - E_{l_{j-1}}\varphi) - U_t\varphi \Big|^2 d\omega \longrightarrow 0$$

as the net determined by the points $(l_0, l_1, \ldots, l_J)$ becomes "indefinitely fine" in an arbitrary interval of the l-axis. It follows from a corollary of the Riesz-Fischer Theorem that a set $\Omega_1 \subset \Omega$ exists having $\int_{\Omega_1} \rho d\omega = \int_{\Omega} \rho d\omega$, at every point A of which

$$U_t(A) = \lim \sum_{j=1}^{J} e^{itl_j} [E_{l_j}\varphi(A) - E_{l_{j-1}}\varphi(A)]$$

as the set of values $(l_0, l_1, \ldots, l_j)$ is replaced successively by the members of a sequence of sets, which sequence forms a properly chosen sub-sequence of the totality of sets considered in the previous formula. In particular, since the values on Ω of the dynamical variables q_k and p_k are among the points of $\mathfrak{H}$, it follows that throughout such a set Ω_1 these variables may be represented as limits of trigonometrical sums of the above type.

An evident property of U_t is that, for an arbitrary single-valued function of several variables, F,

$$U_t F(\varphi_1, \varphi_2, \ldots) = F(U_t\varphi_1, U_t\varphi_2, \ldots),$$

an equation which plays an important part in the developments of our theory.

If φ is a characteristic function of U_t : $U_t\varphi = e^{i\lambda t}\varphi$, it will follow from the preceding equation with $F(\varphi) = |\varphi|$ that $U_t|\varphi| = |U_t\varphi| = |\varphi|$; and hence, when $P|\varphi|$ is defined, $P|\varphi| = 0$; thus $|\varphi|$, which remains constant along the path curves of S_t, has the property of a single-valued integral of the equations of motion. In the important case where no such integral exists we may take $\varphi = e^{i\theta}$. Then $\theta = \theta(A)$ is a real function on Ω, in general infinitely multiply-valued, its branches differing by multiples of 2π, each branch being measurable; and since $U_t\varphi = e^{iU_t\theta} = e^{i\lambda t + i\theta}$, we shall have $U_t\theta = \theta + \lambda t$ and when $P\theta$ is defined, $P\theta = \lambda$. Thus, φ and θ are *analytic* along each given path curve. If they are continuous throughout Ω, θ = const. would represent a "surface of section" of the dynamical system.

If $\varphi_1, \ldots, \varphi_k$ are characteristic functions corresponding to the characteristic numbers $\lambda_1, \ldots, \lambda_k$, we shall have for any set of integers $m_1, \ldots, m_k$,

$$\begin{aligned} U_t(\varphi_1^{m_1} \ldots \varphi_k^{m_k}) &= (U_t\varphi_1)^{m_1} \ldots (U_t\varphi_k)^{m_k} \\ &= e^{i(m_1\lambda_1 + \ldots + m_k\lambda_k)}\, \varphi_1^{m_1} \ldots \varphi_k^{m_k}, \end{aligned}$$

so that $\varphi = \varphi_1^{m_1} \ldots \varphi_k^{m_k}$ (if it is in $\mathfrak{H}$, as will be true if, as above, $\varphi_j = e^{i\theta_j}$) is a characteristic function of characteristic number $\lambda = m_1\lambda_1 + \ldots + m_k\lambda_k$. If in particular there is the Diophantine relation $m_1\lambda_1 + \ldots + m_k\lambda_k = 0$, φ will be an integral in the above sense of the equations of motion. Hence, in the non-integrable case, $\varphi_1^{m_1} \ldots \varphi_k^{m_k}$ = constant; hence, if the λ's have the "basis" $\lambda_1, \ldots, \lambda_h$: $\lambda_j = m_1^j\lambda_1 + \ldots + m_h^j\lambda_h$, we have $\varphi_j = l\varphi_1^{m_1 j} \ldots \varphi_h^{m_h j}$.

In the case where U_t has a pure point spectrum, the characteristic functions form a complete system, and the formula $U_t\varphi = \int_{-\infty}^{\infty} e^{i\lambda t} dE_\lambda \varphi$ above provides us with a trigonometrical series convergent in the mean on Ω by means of which to represent the coördinates and momenta (q, p).

A study is made of the structure of E_t in the general case, with a view to relating the dynamical properties with the structure of the spectrum. In particular, the group of unitary transformations V of $\mathfrak{H}$ is considered which transform E_t as follows: $VE_tV^{-1} = E_{t+\sigma}$. Various generalizations of the above results are made.

[1] Cf. J. v. Neumann, *Math. Annalen*, **102**, 49–131 (1929).

[2] Cf. M. H. Stone, these PROCEEDINGS, **16**, 173–174 (1930).

THE ORDER OF VANISHING OF THE DETERMINANT OF A CONJUGATE BASE

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In the present note I shall use the terminology of the paper entitled, "Sturm Separation and Comparison Theorems in n-Space."[1] In particular see §4 of that paper for the definition of a *conjugate family of secondary extremals*.

I shall prove the following theorem of which an erroneous proof is given in a paper[2] entitled, "The Foundations of a Theory of the Calculus of Variations in the Large in m-Space" (First paper) § 7.

THEOREM. *If $D(x)$ is the determinant of a conjugate base the order of its vanishing at $x = 0$ equals the nullity s of $D(0)$.*

We suppose $s > 0$.

Suppose $\| y_{ij}(x) \|$ is the n-square matrix whose columns are the solutions of the given base.

There exist s linearly independent solutions of the family (that is, solutions dependent on the given base) which vanish at $x = 0$, and no more. Without loss of generality we can suppose the first s columns of $\| y_{ij}(x) \|$ are these vanishing solutions. For one could take a new base for the family for which this would be the case.

The last n-s columns of $\| y_{ij}(x) \|$ will then be of rank n-s at $x = 0$, for otherwise we could obtain additional independent solutions vanishing at $x = 0$ dependent on these last n-s columns. From each of the first s columns we can factor out an x and so write

$$D(x) = x^s E(x).$$

I say that $E(0) \neq 0$. For $E(0)$ is the determinant obtained from $| y_{ij}(x) |$ by differentiating the first s columns and then putting $x = 0$ in all columns, and we shall find that its vanishing is impossible.

Using the summation convention of tensor analysis set

$$c_j y_{ij}(x) = u_i(x) \qquad (i = 1, \ldots, n \;\; j = 1, \ldots, s)$$
$$c_h y_{ih}(x) = z_i(x) \qquad (i = 1, \ldots, n; \;\; h = s + 1, \ldots, n).$$

If $E(0)$ were zero we could determine constants $c_1, \ldots, c_n$, not all zero, such that

$$u_i'(0) = z_i(0). \qquad (i = 1, \ldots, n)$$

I say that $[z(0)] \neq [0]$.

If $[z(0)]$ were null it would follow that $c_{s+1}, \ldots, c_n$ would be zero since the rank of the last n-s columns of $E(0)$ is n-s.

We would, moreover, have

$$u_i'(0) = u_i(0) = 0 \qquad (i = 1, \ldots, n)$$

so that $[u(x)]$ would be identically null contrary to the assumption that the solutions of the base are linearly independent. Thus $[z(0)] \neq [0]$.

Now the solutions $u_i(x)$ and $z_i(x)$ are conjugate. If we use the fact that $[u(0)] = [0]$ the condition that $u_i(x)$ and $z_i(x)$ be conjugate solutions takes the form,[3]

$$R_{ik}(0)z_i(0)u_k'(0) = R_{ik}(0)z_i(0)z_k(0) = 0. \qquad (i, k = 1, \ldots, n)$$

But this is contrary to the assumption that the problem is positively regular.

Thus $E(0) \neq 0$ and the order of $D(x)$ at $x = 0$ equals the nullity s of $D(0)$.

[1] "A Generalization of the Sturm Separation and Comparison Theorems in n-Space," *Math. Ann.*, **103**, 52–69 (1930).

[2] "The Foundations of the Calculus of Variations in the Large in m-Space. (First paper.) *Trans. Am. Math. Soc.*, **31** (1930). Lemma § 7, p. 385. Lemma 2 of p. 387 should read, "Let $D(x)$ be a determinant whose n columns are n conjugate, etc."

The error in the proof in § 7 was first called to my attention by G. A. Bliss. The proof given in § 7 can be modified so as to be correct but the present proof seems simpler.

[3] See Bolza, *Variationsrechnung*, p. 626.

AUTOMORPHISMS OF ORDER 2 OF AN ABELIAN GROUP

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1. INVARIANT AUTOMORPHISMS OF ORDER 2. It is known that an invariant operator of the group of isomorphisms of an abelian group G must transform every operator of G into the same power of itself. Hence it results that when the order of G is of the form p^m, where p is an odd prime number, its group of isomorphisms involves one and only one invariant operator of order 2. When $p = 2$ this group of isomorphisms contains no invariant operator of order 2, one invariant operator of this order, or three such operators as G involves no operator of order 4, operators of order 4 but none of order 8, or operators of order 8. If we combine these facts with the known theorem that the group of isomorphisms of every abelian

group is the direct product of the groups of isomorphisms of its Sylow subgroups there results the following theorem: *The number of the invariant operators of order* 2 *under the group of isomorphisms of an abelian group is* $2^k - 1$, *where k is the number of the distinct prime numbers which divide the order of the group when this order is either odd or when the group involves operators of order* 4 *but none of order* 8. *When this group involves operators of order* 8 *k is one larger than the numbers of these primes and when it involves operators of order* 2 *but none of order* 4, *k is one less than this number.*

2. NON-INVARIANT AUTOMORPHISMS OF ORDER 2. In every automorphism of order 2 of an abelian group G of odd order it is possible to find two subgroups such that every operator of one of them corresponds to itself while every operator of the other corresponds to its inverse and that G is the direct product of these two subgroups. It may be noted that when an abelian group is the direct product of two subgroups than either both of these subgroups are characteristic or neither of them has this property. This results directly from the fact that every characteristic proper subgroup of an abelian prime power group must include the fundamental characteristic subgroup thereof. From the same theorem it follows that an abelian prime power group cannot be the direct product of two or more of its characteristic proper subgroups. Hence it results that if an abelian group is the direct product of characteristic proper subgroups, then all of these subgroups are either Sylow subgroups or the direct products of Sylow subgroups of the entire group.

A necessary and sufficient condition that an automorphism of order 2 of G is invariant under the group of isomorphisms of G is that the two related subgroups are characteristic. Since both of these subgroups must be non-characteristic in a non-invariant automorphism of order 2 there must be some odd prime number p which divides both of their orders. Each of the sets of reduced independent generators of these two subgroups must therefore involve at least one operator whose order is divisible by p. If this operator is multiplied successively by the first p different powers of the operator of order p generated by an independent generator of the other set while the remaining independent generators of these two sets remain unchanged there result p different sets of independent generators of G. The generators of one of these two subgroups remain unchanged and hence this subgroup remains unchanged. In the case of the other subgroup the generators are changed and also the p subgroups are different as otherwise they would involve an operator of order p from the unchanged subgroup. It therefore results that *every complete set of conjugate operators of order* 2 *of the group of isomorphisms of an abelian group of odd order involves at least* p^2 *distinct operators if it involves more than one, where p is a prime divisor of the order of the group.*

When the order of G is of the form 2^m, there may be complete sets of

conjugate operators of order 2 under the group of isomorphisms of G such that each of the sets involves only two elements. It is easy to prove that there are always at least two such sets whenever G has two and only two largest invariants, and these exceed 4. When this condition is satisfied G contains a characteristic subgroup H of index 4 composed of all its operators which are not of highest order. There are two automorphisms of order 2 of G in which H is composed of all the operators which correspond to themselves and in which no cyclic subgroup of highest order corresponds to itself. These therefore constitute a complete set of conjugates under the group of isomorphisms of G. A second such complete set results when H is composed of all the operators of G which correspond to their inverses under an automorphism of order 2 and hence the inverse commutator subgroup of G is its characteristic subgroup of order 4.

3. CYCLIC COMMUTATOR SUBGROUPS OF A GROUP OF ORDER 2^m. A necessary and sufficient condition that an automorphism is of order 2 is that every commutator which arises from this automorphism corresponds to its inverse thereunder. Hence it results that if G is any abelian group of order 2^m and if H is any subgroup of G which gives rise to a cyclic quotient group, then a necessary and sufficient condition that G admits an automorphism of order 2 in which H is composed of all its operators which correspond to themselves is that the co-set of G which corresponds to the square of an independent generator of this quotient group involves operators whose order is equal to that of this generator. The number of these operators is equal to the number of the automorphisms of order 2 of G in which H is composed of all the operators of G which correspond to themselves thereunder, since this number is equal to twice the number of the cyclic subgroups of this order generated by these operators and each such subgroup gives rise to two such automorphisms of order 2. The number of the automorphisms of order 2 of G which are characterized by the fact that H is composed of all the operators of G which correspond to themselves under each of them may also be found as follows: If the co-set which corresponds to the square of an independent generator of the quotient group involves no operator whose order is less than the order of this generator, then this number is equal to the number of the operators of H whose orders do not exceed the order of this quotient group. On the other hand, if this co-set involves operators whose order is less than the order of this quotient group, then the number of these automorphisms of order 2 is equal to the number of the operators of H whose order is equal to the order of the quotient group in question. These results follow directly from the fact that in the latter case an operator of lowest order in this co-set can be taken as an independent generator of the subgroup of G corresponding to a subgroup of index 2 of this quotient group, while in the former case any operator of this co-set whose order is equal to the order of this quotient

group can be used as such a generator. *It is always possible to choose a set of independent generators of G so that all except at most three of its elements appear in H.*

By means of the results of the two preceding paragraphs it is easy to determine the number of the automorphisms of order 2 of G which correspond to cyclic commutator subgroups. For this purpose it is only necessary to find successively all the subgroups of G which give rise to such cyclic quotient groups that the co-set corresponding to the square of an independent generator of this quotient group involves an operator whose order is equal to the order of this generator, and then to count the number of the corresponding automorphisms of order 2 by either of the two methods noted above. It also results from these paragraphs that an independent generator of the commutator subgroup corresponding to an automorphism of order 2 cannot be a fourth power of an operator of G when the order of this generator exceeds 2, and that when such a generator is a square of an operator of G then this operator must be transformed under this automorphism into a power of itself. It must therefore be then transformed either into its inverse or into its semi-inverse, the semi-inverse of an operator of order 2^α being its $2^{\alpha-1}-1$ power. *The independent generators of the commutator subgroup corresponding to an automorphism of order 2 of G must be either non-squares or squares of non-squares of G whenever their orders exceed 2.*

4. COMMUTATOR SUBGROUPS OF TYPE (1, 1, 1...) OF A GROUP OF ORDER 2^m. When the subgroup H composed of all the operators of an abelian group G of order 2^m which correspond to themselves under an automorphism of order 2 gives rise to an abelian quotient group of type (1, 1, 1...) then H must involve at least one subgroup which is simply isomorphic with this quotient group. The number of such automorphisms for a given H is equal to the product of the number of such subgroups contained in H and the order of the group of isomorphisms of one of these subgroups. By considering successively all the subgroups of G which give rise to such quotient groups we can obtain the total number of the possible automorphisms of order 2 of G which give rise only to commutators whose orders divide 2. It is, however, often more convenient to determine this number by another method which we proceed to explain.

Suppose that G has α invariants of which β exceed 2 and let H_0 be any subgroup of G which satisfies the following conditions: It is of type (1, 1, 1...), it includes the subgroup of order 2^β of G which is generated by its operators of order 2 which are squares, its order is 2^γ. We proceed to find the number of the automorphisms of order 2 of G giving rise to commutator subgroups of type (1, 1, 1...) and whose invariant operators of order 2 are those contained in H_0. This implies that H_0 contains at least one subgroup whose order is $2^{\alpha-\gamma}$. For each such subgroup we may establish as many automorphisms of order 2 of the subgroup of order 2^α generated by

the operators of order 2 in G as the order of the group of isomorphisms of this subgroup. Moreover, every operator whose order exceeds 2 in a given set of independent generators of G may be transformed into itself multiplied by any one of the operators of H_0. When $\alpha > \gamma$ the number of these automorphisms of order 2 corresponding to a fixed H_0 is therefore equal to the product of the following three numbers: $2^{\beta\gamma}$, the number of the subgroups of order $2^{\alpha-\gamma}$ contained in H_0, the order of the group of isomorphisms of such a subgroup. When $\alpha = \gamma$ this product must be diminished by unity on account of the identity automorphism.

5. COMMUTATOR SUBGROUPS ARISING FROM AUTOMORPHISMS OF ORDER 2 OF AN ABELIAN GROUP OF ORDER 2^m. Let H be the subgroup composed of all the operators of an abelian group G of the order 2^m which correspond to themselves under an automorphism of order 2 of G and suppose that the operators of G are arranged in co-sets with respect to H in such a way that the commutators of highest order appear last. To a subgroup of index 2 of G there then corresponds a subgroup of index 2 of the commutator subgroup such that all the commutators which do not appear therein are of highest order. As the given subgroup of index 2 of G cannot involve all its operators of highest order it results that it is always possible to select the operators of a set of reduced independent generators of an abelian group and of the commutator subgroup arising from any automorphism of this group in such a way that an independent generator of highest order of the group gives rise to an independent generator of highest order of the related commutator subgroup.

While we *may* select any operator of highest order which does not appear in the given subgroup of index 2 of G as an operator of a set of reduced independent generators of G we *must* select such an operator s of lowest order to obtain such a set, and all of the remaining operators of the set may always be chosen from the operators of this subgroup. The operators of a set of reduced independent generators of the commutator subgroup arising from the said automorphism of order 2 of G may then be so chosen that s gives rise to an operator of highest order c in the set. The order of c can clearly not exceed the order of s and it may be equal to one-half of this order. Since c and s^{-2} appear in the same co-set of G with respect to H it results that *if s is an independent generator of lowest order of an abelian group of order 2^m which gives rise to a commutator c of highest order under an automorphism of order 2 then the order of c must be one of the following five numbers: the order of s, one half of this order, the order of a smaller independent generator of the group, twice this order, or 2.*

In every automorphism of order 2 of any abelian group G the operators which correspond to their inverses constitute a subgroup K of G which includes the commutator subgroup of G. A necessary and sufficient condition that G is the direct product of K and its subgroup H composed of

the operators which correspond to themselves under this automorphism is that the order of G is odd. This is also a necessary and sufficient condition that G is the direct product of K and C. When the order of G is of the form 2^m the number of the invariants of K is the same as the number of the invariants of H and at least equal to the number of the invariants of C, and the group generated by H and C contains the square of all the operators of G and is of index 2^i under G, where i represents the number of the invariants of C. Hence the order of the cross-cut of C and H is 2^i. When either H or K is cyclic then the three subgroups H, K and C must be cyclic and their common cross-cut is of order 2. If this condition is satisfied and G is also decomposable into H and K there are $m/2 - 1$ or $(m - 1)/2$ such groups as m is even or odd.

[1] G. A. Miller, *Trans. Amer. Math. Soc.* **10**, 472, (1909).

ON THE UNIFIED FIELD THEORY. VI

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Let us suppose that the functions h_1^i in group G_0 have the values δ_1^i throughout a finite region R of the four dimensional continuum; these special values of the h_1^i can obviously be imposed, at least throughout a sufficiently small region of the continuum, by a suitable coördinate transformation. A coördinate system for which the h_1^i have the above special values will be referred to as a *cannonical coördinate system*. Interpreting the coordinate x^1 as the time t let us now assume that a disturbance is produced at a time $t = 0$ throughout a closed region R_0 of space.[1] After a time $t = \varphi(x^2, x^3, x^4)$, the effect of this disturbance will be felt at a point (x^2, x^3, x^4) outside the region R_0. For a definite value of t the equation $\varphi(x^2, x^3, x^4) = t$ will represent the surface of the space (x^2, x^3, x^4) which, at the instant t, separates the region affected from the region unaffected by the disturbance. If we assume that the values of the h_α^i and their derivatives vary in a continuous manner when we pass from one region to the other, then it follows from the result in sect. 8 of Note V under the hypothesis of canonical coördinates that the surface $t - \varphi(x^2, x^3, x^4) = 0$ must be a characteristic surface of the field equations. Wave surfaces are thus identified with the characteristic surfaces.

Now assume the expression for the element of distance in the region R in the form

$$ds^2 = dt^2 - \sum_{\alpha=2}^{4} \sum_{\beta=2}^{4} \gamma_{\alpha\beta}\, dx^\alpha\, dx^\beta \qquad (a)$$

where we have put $t = x^1$ and $\gamma_{\alpha\beta} = -g_{\alpha\beta}$ in terms of the notation used in previous notes. We shall refer for the moment to the coördinates for which the form (a) of the element of distance is valid as *Gaussian* coördinates in conformity with the terminology used by Hilbert.[2] It will be assumed likewise that the coördinates of a system of Gaussian coördinates have the significance of coördinates of time and space as implied by the above expression for the element of distance. Use has been made of Gaussian coördinates in this sense in recent work on cosomology.[3]

Owing to the special form of the element of distance (a) in Gaussian coördinates the function φ must, therefore, satisfy the equation

$$\sum_{\alpha=2}^{4} \sum_{\beta=2}^{4} \gamma^{\alpha\beta} \frac{\partial\varphi}{\partial x^\alpha} \frac{\partial\varphi}{\partial x^\beta} = 1$$

over the surface $\varphi = t$ where $\gamma^{\alpha\beta}$ is the cofactor of the element $\gamma_{\alpha\beta}$ in the determinant $|\gamma_{\alpha\beta}|$ divided by this determinant. The equation

$$\varphi(x^2, x^3, x^4) = \text{const.} \qquad (b)$$

therefore represents a family of parallel surfaces, and hence *the successive positions of the wave front form a family of parallel surfaces which are propagated with unit velocity.*

The hypersurface formed from the totality of bicharacteristics issuing from a point P is a characteristic surface (see Sect. 4 of Note IV). Let us denote the sheet of this hypersurface corresponding to IV (4.11) by S; let us also denote the surface of intersection of S with the hypersurface $t = \text{const.}$ by S*. It can be shown that *from the given position R_0 of the wave at time $t = 0$, the position of the wave (b) at any later time t can be obtained by taking the envelope of the surfaces S* corresponding to the different points of R_0.*[4] In other words Huygen's principle can be applied for the construction of the wave fronts. A discussion of wave surfaces in general from this point of view has lately been made on the basis of contact transformations by L. P. Eisenhart.[5]

In particular if the surface R_0 reduces to a point P the corresponding wave surface (b) assumes the form

$$(w^2)^2 + (w^3)^2 + (w^4)^2 = \text{const.} \qquad (c)$$

in a system of metric local coördinates with origin at P. The invariance of (c) under orthogonal rotations of the fundamental vectors h_i^α, i.e. Lorentz transformations of the metric local coördinates, has its interpretation in the experimental fact that the velocity of light is independent of the motion of the source or the observer.

The orthogonal trajectories of the family of wave surfaces (b) are *light rays* in the usual sense; these curves, however, are *geodesics of zero length*[6] when considered with respect to the Gaussian coördinates (t, x^2, x^3, x^4). This establishes the geodesics of zero length or bicharacteristics of the field equations as the light tracks in the unified field theory.

A treatment of the problems of optics can be made on the basis of the above theory of gravitational and electromagnetic waves. In fact, a step in this direction has recently been taken by Synge and McConnell[7] who have deduced formulae for the angle of reflection and refraction of light from a moving surface by a method adaptable to the point of view of the present theory. Other interesting problems in geometrical and physical optics await investigation from this standpoint.

1. We shall add to this note a brief discussion of the problem of the determination of the structure of the continuum by the assignment of data in a system of local coördinates. Let us define a three-dimensional variety S_3 and a two-dimensional variety S_2 in a system of affine local coördinates z^i by

$$S_3 : \Phi(z^1, \ldots, z^4) = 0, \; S_2 : \begin{cases} \Phi(z^1, \ldots, z^4) = 0 \\ \Psi(z^1, \ldots, z^4) = 0 \end{cases}$$

where the functions Φ and Ψ are assumed to be analytic in the neighborhood of the origin. We shall suppose that Φ and Ψ are independent as functions of z^1 and z^2; this causes no loss of generality as it involves at most a relettering of the coördinate axes. Now put

$$x^1 = \Phi(z), \; x^2 = \Psi(z), \; x^3 = z^3, \; x^4 = z^4. \tag{1.1}$$

This defines an analytic transformation of coördinates which possesses a unique inverse in the neighborhood of the origin of the local system.

We shall say that the origin of the *local coördinate system is a characteristic point with respect to the hypersurface S_3 if the expression*

$$\left(\frac{\partial\Phi}{\partial z^1}\right)^2 - \left(\frac{\partial\Phi}{\partial z^2}\right)^2 - \left(\frac{\partial\Phi}{\partial z^3}\right)^2 - \left(\frac{\partial\Phi}{\partial z^4}\right)^2$$

vanishes at the origin of these coördinates. Our discussion will be divided into two parts: (A) the case for which the origin is a characteristic point, and (B) the case for which the origin is not a characteristic point with respect to the hypersurface S_3. We shall refer to these two cases as hypothesis (A) and hypothesis (B), respectively.

Now suppose that the quantities K^*_{l1} defined in Note III are given over S_3 and the K^*_{l2} over S_2; this can, in fact, be accomplished by taking the K^*_{l1} to be analytic functions of the coördinates (x^2, x^3, x^4) and the K^*_{l2} as analytic functions of the coördinates (x^3, x^4), i.e., analytic in the neighbor-

hood of the values x_0^α corresponding to the origin of the local system. Now observe that the coefficients H of the power series expansions I (2.10) are uniquely determined on account of (1.1). Hence, if we know the derivatives at x_0^α of the h_α^i and K_{lm}^* up to the order r inclusive, the derivatives of the h_α^i of order $r+1$ at x_0^α will be determined by II (4.2). Differentiation of III (3.3) under hypothesis (A) leads to the determination at x_0^α of the derivatives of the K_{lm}^* of order $r+1$, etc. By this process we obtain uniquely determined convergent power series expansions[8] of the $h_\alpha^i(x)$ in the neighborhood of the point x_0^α; transformation by means of (1.1) gives the functions h_α^i in the affine local coördinate system. As a matter of fact the functions h_α^i are likewise uniquely determined in the system of metric local coördinates having its origin coincident with the origin of the affine local coördinates and we, therefore, arrive at the following

EXISTENCE THEOREM. *The specification of the functions K_{l1}^* and K_{l2}^* over the varieties S_3 and S_2, respectively, as analytic functions of the surface coördinates determines uniquely a set of analytic integrals h_α^i of the field equations in a system of affine (or metric) local coördinates having its origin at a point P on S_2 not characteristic with respect to S_3.*

In particular we can take $\Phi = z^1$ and $\Psi = z^2$. We then arrive at a theorem which on the point of view of our previous notes can be stated roughly as follows: *The specification at a particular instant $t = 0$ of the absolute electromagnetic forces K_{lm}^* throughout a small region R_0 determines the structure of the space-time continuum in the neighborhood of R_0.*

2. A modification of the above existence theorem is necessary when the hypothesis (B) is adopted. We can suppose that the functions Φ and Ψ satisfy the normal conditions C_1 and C_2 at a point P as explained in Sect. 1 of Note V. Taking the point P as the origin of a system of affine local coördinates z^i we shall then have

$$\left.\begin{aligned} &\frac{\partial\Phi}{\partial z^1}\frac{\partial\Psi}{\partial z^1} - \frac{\partial\Phi}{\partial z^2}\frac{\partial\Psi}{\partial z^2} - \frac{\partial\Phi}{\partial z^3}\frac{\partial\Psi}{\partial z^3} - \frac{\partial\Phi}{\partial z^4}\frac{\partial\Psi}{\partial z^4} \gtrless 0, \quad \frac{\partial\Phi}{\partial z^2} \gtrless 0, \\ &\frac{\partial\Phi}{\partial z^1}\frac{\partial\Psi}{\partial z^2} - \frac{\partial\Psi}{\partial z^2}\frac{\partial\Psi}{\partial z^2} \gtrless 0, \quad \frac{\partial\Phi}{\partial z^3}\frac{\partial\Psi}{\partial z^4} - \frac{\partial\Phi}{\partial z^4}\frac{\partial\Psi}{\partial z^3} \gtrless 0 \end{aligned}\right\} \tag{2.1}$$

at the origin of these coördinates. At the point x_0^α of the (x) coördinate system defined by (1.1) the inequalities V (1.7) will, therefore, be satisfied. Call S_3^* the surface defined by $\Psi = 0$ and consider the functions U and V defined in Sect. 4 of Note V. If we specify the functions U over the hypersurfaces S_3 and S_3^* and the functions V over the surface S_2 as analytic functions of the surface coördinates, we can uniquely determine the successive coefficients of the power series expansions[8] of the components

h^i_α about the point x^α_0 by applying the method of the preceding section to the equations V (4.1), V (4.2) and V (4.3). This gives the following

EXISTENCE THEOREM. *The specification of the functions U over the varieties S_3 and S^*_3 and the functions V over the variety S_2 as analytic functions of the surface coördinates determines uniquely a set of analytic integrals h^i_α of the field equations in a system of affine (or metric) local coördinates having its origin at a point P on S_2 characteristic with respect to S_3 and such that at P the inequalities* (2.1) *are satisfied.*

As mentioned in Note V the normal conditions (2.1) place no restriction on the hypersurface S_3.

[1] Cp. E. Goursat, *Cours d'analyse mathematique*, **3**, 94 (1927).

[2] D. Hilbert, "Die Grundlagen der Physik," *Math. Ann.*, **92**, 1–32 (1924).

[3] See, for example, H. P. Robertson, "On the Foundations of Relativistic Cosmology," *Proc. Nat. Acad. Sci.*, **15** (1929), 822–829, where other references are also given; in particular see footnote 4 to this paper.

[4] Cp. J. Hadamard, *Lecons sur la propagation des ondes, Hermann*, 290 (1903).

[5] L. P. Eisenhart, "Contact Transformations," *Ann. of Math.*, **30**, 211–249 (1929).

[6] Proof of this statement can be based on the discussion in Sect. 2 of Note IV.

[7] J. L. Synge and A. J. McConnell, "Riemannian Null Geometry," *Phil. Mag.*, **5**, 7th Series, 241–263 (1928).

[8] The proof of convergence involved here will possibly be given later in a comprehensive exposition of the present theory.